10/089993
JC15 Rec'd PCT/PTO 04 APR 2002

Derivatives of heterocycles with 5 members, their preparation and their use as medicaments

The present invention relates to the use of compounds of general formula (I) for preparing a medicament intended to inhibit monoamine oxydases (MAO) and/or lipidic peroxidation and/or to act as modulators of the sodium channels. A subject of the invention is also, as medicaments, the compounds of general formula (II) defined hereafter. Moreover it relates to new compounds of general formula (III).

The compounds mentioned above often present 2 or 3 of the activities mentioned above, which confer advantageous pharmacological properties on them.

In fact, taking into account the potentiel role of the MAO's and ROS's ("*reactive oxygen species*", at the origin of lipidic peroxidation) in physiopathology, the new described derivatives corresponding to general formula (I) can produce beneficial or favorable effects in the treatment of pathologies where these enzymes and/or these radicular species are involved. In particular:

- disorders of the central or peripheral nervous system such as for example neurological diseases where Parkinson's disease, cerebral or spinal cord traumatisms, cerebral infarction, sub arachnoid hemorrhage, epilepsy, ageing, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, peripheral neuropathies, pain can in particular be mentioned;
- schizophrenia, depressions, psychoses;
- disorders of the memory and the humour;
- pathologies such as for example migraine;
- behavioural disorders, bulimia and anorexia;
- auto-immune and viral diseases such as for example lupus, AIDS, parasitic and viral infections, diabetes and its complications, multiple sclerosis.
- addiction to toxic substances;

- proliferative and inflammatory pathologies;
- and more generally all the pathologies characterised by an excessive production of ROS's and/or participation of MAO's.

In all of these pathologies, experimental evidence exists which demonstrates the involvement of ROS's (*Free Radic. Biol. Med.* (1996) **20**, 675-705; *Antioxid. Health. Dis.* (1997) **4** (Handbook of Synthetic Antioxidants), 1-52) as well as the involvement of MAO's (Goodman & Gilman's: *The pharmacological basis of therapeutics* , 9th ed., 1995, 431-519).

The advantage of a combination of the inhibitory activities of MAO and inhibition of lipidic peroxidation is for example well illustrated in Parkinson's disease. This pathology is characterized by a loss of dopaminergic neurons of the nigrostriatal route the cause of which would in part be linked to an oxidizing stress due to ROS's. The exogenic dopamine from L Dopa is used in therapeutics in order to maintain sufficient levels of dopamine. MAO inhibitors are also used with L Dopa to avoid its metabolic degradation but do not act on the ROS's. Compounds which act both on MAO's and ROS's will therefore have a certain advantage.

Moreover, the character of the modulator of the sodium channels is very useful for therapeutic indications such as:

- the treatment or prevention of pain, and in particular:
  - post-operative pain,
  - migraine,
  - neuropathic pain such as trigeminal neuralgia, post-herpetic pain, diabetic neuropathies, glossopharyngeal neuralgias, secondary radiculopathies and neuropathies associated with metastatic infiltrations, adiposis dolorosa and pain associated with burns,
  - central pain as a result of vascular cerebral accidents, thalamic lesions and multiple sclerosis, and
  - chronic inflammatory pain or pain linked to a cancer;
- the treatment of epilepsy;
- the treatment of disorders linked to neurodegeneration, and in particular:
  - vascular cerebral accidents,
  - cerebral traumatism, and
  - neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis;

- the treatment of bipolar disorders and irritable colon syndrome.

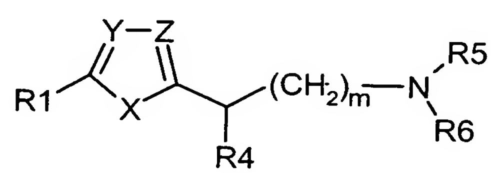
The concrete advantages of the presence in a compound of at least one of these activities is therefore clearly apparent from the above.

The European Patent Application EP 432 740 describes derivatives of hydroxyphenylthiazoles, which can be used in the treatment of inflammatory diseases, in particular rheumatic diseases. These derivatives of hydroxyphenylthiazoles show properties of trapping free radicals and inhibitors of the metabolism of arachidonic acid (they inhibit lipoxygenase and cyclooxygenase).

Other derivatives of hydroxyphenylthiazoles or hydroxyphenyloxazoles are described in the PCT Patent Application WO 99/09829. These have analgesic properties.

A certain number of derivatives of imidazoles with close or identical structures to those of the compounds corresponding to general formula **(I)** according to the invention have moreover been described by the Applicant in the PCT Patent Application WO 99/64401 as agonists or antagonists of somatostatin. However, said derivatives of imidazoles have therapeutic properties in fields different from those indicated above (suppression of the growth hormone and the treatment of acromegalia, treatment of the recurrence of stenosis, inhibition of the secretion of gastric acid and prevention of gastro-intestinal bleeding in particular).

Moreover, the compounds of general formula **(A1)**



(A1)

in which

R1 represents one of the aryl, heteroaryl, aralkyl or cycloalkyl radicals optionally substituted by one to three substituents chosen independently from a halogen atom, the CF_3, CN, OH, alkyl or alkoxy radical, SO_2R9 with R9 representing NH_2 or $NHCH_3$;

X represents NR2, R2 representing H or alkyl;

Y represents N or CR3;

Z represents CR3 or N;

on the condition however that Y and Z are not both CR3 or N at the same time;

R3 represents H, alkyl, halogen, hydroxyalkyl or phenyl optionally substituted by 1 to 3 substituents chosen from H, CF_3, CN, SO_2NH_2, OH, alkyl or alkoxy;

m represents 0, 1 or 2;

R4 represents H or alkyl;

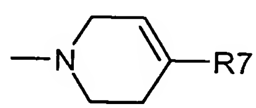
when Z represents CR3, then R3 and R4 can also represent together $-(CH_2)_{n1}-$ with n1 an integer from 2 to 4 or R2 and R4 can also represent together $-(CH_2)_{n2}-$ with n2 an integer from 2 to 4;

R5 and R6 represent independently H, alkyl, alkoxy, aryl or aralkyl;

NR5R6 can also represent together (in particular):

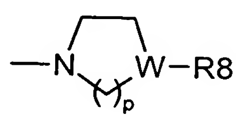
- the optionally substituted 2-(1,2,3,4-tetrahydroquinolyl) radical,

- a



radical in which R7 represents one of the phenyl, benzyl or phenethyl radicals in which the phenyl ring can be substituted;

- a



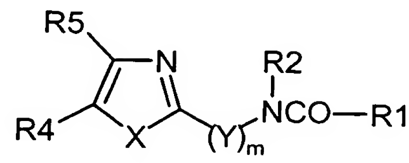
radical in which p is an integer from 1 to 3,

W is N and R8 represents H, CF_3, one of the phenyl, pyridyl or pyrimidinyl radicals optionally substituted once to twice by radicals chosen from halogen, OH, alkyl or alkoxy, or

W is CH and R8 represents phenyl optionally substituted or aralkyl optionally substituted on the aryl group;

have been described in the PCT Patent Application WO 96/16040 as partial agonists or antagonists of the dopamine sub-receptors of the brain or as prodrug forms of such partial agonists or antagonists. Therefore these compounds would have useful properties in the diagnosis and treatment of affective disorders such as schizophrenia and depression as well as certain disorders of movement such as Parkinson's disease.

It has also been described in the PCT Patent Application WO 98/27108 that certain amides of general formula **(A2)**



(A2)

in which:

R1 represents in particular an alkyl, optionally substituted phenyl or optionally substituted heterocyclic aryl radical;

R2 represents H or phenylalkyl;

R4 represents H, quinolyl, 3-4-methylenedioxyphenyl or one of the phenyl or pyridyl radicals optionally substituted, by a radical or radicals chosen in particular from alkyl, alkoxy, alkylthio, optionally protected hydroxy, amino, alkylamino, dialkylamino;

R5 represents H or an imidazolyl, phenyl, nitrophenyl, phenylalkyl radical, or also a –CO-N(R7)(R8) radical, in which R7 and R8 represent independently H, phenyl, phenylalkyl, alkyl or alkoxy;

or R4 and R5 in combination form a group of formula -CH=CH-CH=CH-;

Y is a phenylene radical substituted by a phenyl, phenoxy or phenylalkoxy radical, or a group of formula –CH(R3)-, in which R3 represents H or a radical of formula $-(CH_2)_n-$R6, in which R6 represents an optionally protected hydroxy, acyl, carboxy, acylamino, alkoxy, phenylalkoxy, alkylthio, optionally substituted phenyl, optionally substituted pyridyl, pyrazinyl, pyrimidinyl, furyl, imidazolyl, naphthyl, N-alkylindolyl or 3,4-methylenedioxyphenyl radical and n is an integer from 0 to 3;

R2 and R3 taken together with the carbon atoms which carry them can form a phenyl group;

X represents S or NR9;

R9 representing H, an alkyl or cycloalkyl radical, or also a benzyl radical optionally substituted once on its phenyl part by H, alkyl or alkoxy;

are inhibitors of the NO synthases and can be used to treat diseases which include in particular cardiovascular or cerebral ischemia, cerebral hemorrhage, disorders of the central nervous system, Alzheimer's disease, multiple sclerosis, diabetes, hepatitis, migraine, rheumatoid arthritis and osteoporosis.

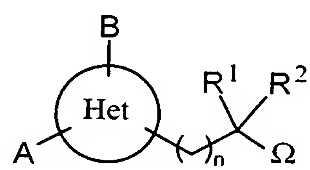
In a different field, the Applicant has itself previously described in the PCT Patent Application WO 98/58934 derivatives of amidines having the ability to inhibit NO synthases and/or lipidic peroxidation.

The Applicant has now unexpectedly discovered that certain intermediates of the first stages of synthesis of the amidines described in the PCT Patent Application WO 98/58934, and more generally certain derivatives of heterocycles with five members, namely the products of general formula **(I)** defined hereafter, have at least one of the three properties chosen from the following properties (and often even two of these three properties even sometimes all three at the same time):

- MAO inhibition properties;
- lipidic peroxidation inhibition properties; and
- properties of modulating the sodium channels.

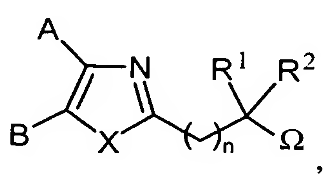
These advantageous properties offer the advantage of opening up numerous uses for such compounds, in particular in the treatment of neurodegenerative diseases, and in particular those indicated previously, of pain or of epilepsy.

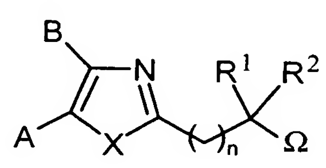
According to the invention, the compounds corresponding to general formula **(I)**



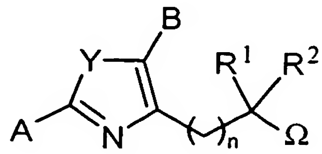
(I)

in racemic, enantiomeric form or any combination of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula **(I)** corresponds exclusively to one of the following sub-formulae:

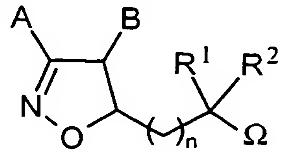




(I)$_1$ **(I)$_2$**



and

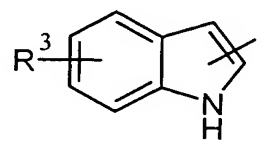


(I)$_3$ (I)$_4$

in which

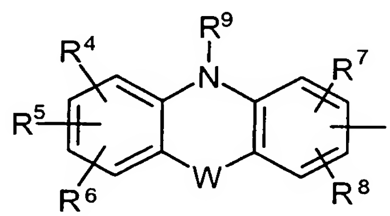
A represents

either a



radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

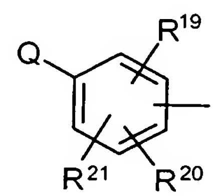
or a



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or $NR^{10}R^{11}$ radical,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical,
R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group

constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^9 represents a hydrogen atom, an alkyl radical or a $-COR^{15}$ group,
R^{15} representing a hydrogen atom or an alkyl, alkoxy or $NR^{16}R^{17}$ radical,
R^{16} and R^{17} representing, independently, a hydrogen atom or an alkyl radical, or R^{16} and R^{17} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$, in which R^{18} represents a hydrogen atom or an alkyl radical;

either a



radical in which Q represents H, $-OR^{22}$, $-SR^{22}$, $-NR^{23}R^{24}$, a phenyl radical optionally substituted by one or more substituents chosen independently from a halogen atom, an OH, cyano, nitro, alkyl, alkoxy or $-NR^{10}R^{11}$ radical and a group with two substituents representing together a methylenedioxy or ethylenedioxy radical, or also Q represents a -COPh, $-SO_2Ph$ or $-CH_2Ph$ radical, said -COPh, $-SO_2Ph$ or $-CH_2Ph$ radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^{12} representing a hydrogen atom, an alkyl or alkoxy or $NR^{13}R^{14}$ radical,
R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group

constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

R^{22} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

R^{23} and R^{24} representing, independently, a hydrogen atom, an alkyl radical or a -CO-R^{25} radical,

R^{25} representing an alkyl radical,

and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,

R^{26} representing a hydrogen atom or an alkyl radical,

R^{27} and R^{28} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{29}$ group, or R^{27} and R^{28} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,

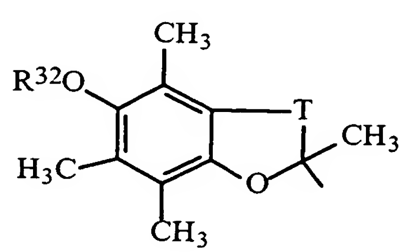
q representing an integer from 0 to 2,

R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

R^{29} representing a hydrogen atom, an alkyl, alkoxy or $-NR^{30}R^{31}$ radical,

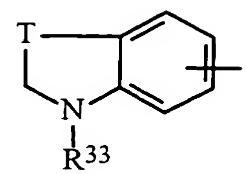
R^{30} and R^{31} representing, independently, a hydrogen atom or an alkyl radical, or R^{30} and R^{31} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical, and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,

Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms, R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical, R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals, R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical, R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine, and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^{38},
R^{38} representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, $-(CH_2)_g-Z^1R^{39}$, $-(CH_2)_g-COR^{40}$, $-(CH_2)_g-NHCOR^{70}$, aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radical, the aryl group of the aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radicals itself being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^2R^{39}$ or $-(CH_2)_k-COR^{40}$ radicals,

Z^1 and Z^2 representing a bond, -O-, $-NR^{41}-$ or -S-,

R^{39} and R^{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{42}R^{43}$ radical,

R^{42} and R^{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^2 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl or $-(CH_2)_g-NHCOR^{71}$ radical, or also one of the aralkyl or heteroarylalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkoxy, hydroxy, cyano, nitro, amino, alkylamino or dialkylamino radical,

R^{70} and R^{71} representing independently an alkyl or alkoxy radical;

or R^1 and R^2, taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a $-(CH_2)_g-Z^3R^{44}$ radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z^3 representing a bond, -O-, $-NR^{45}-$ or -S-,

R^{44} and R^{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the $NR^{46}R^{47}$ or OR^{48} radicals, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl,

$-(CH_2)_g-Z^4R^{50}$, $-(CH_2)_k-COR^{51}$, $-(CH_2)_k-COOR^{51}$, $-(CH_2)_k-CONHR^{51}$ or $-SO_2R^{51}$ radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl and in particular pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^5R^{50}$, $-(CH_2)_k-COR^{51}$ and $-(CH_2)_k-COOR^{51}$,

Z^4 and Z^5 representing a bond, -O-, $-NR^{52}-$ or -S-,

or R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S- and -CO-, said heterocycle being able to be for example an azetidine, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine,

R^{50} and R^{52}, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{51} representing, independently each time that they occur, a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical has 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, alkoxyalkyl or $NR^{58}R^{59}$ radical, or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical,

R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{53} and R^{54} representing, independently, a hydrogen atom or a $-(CH_2)_k-Z^7R^{60}$ or $-(CH_2)_k-COR^{61}$ radical,

Z^7 representing a bond, -O-, $-NR^{62}-$ or -S-,

R^{60} and R^{62} representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, $-(CH_2)_k-Z^8R^{63}$ and $-(CH_2)_k-COR^{64}$ radicals,

R^{61} representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{65}R^{66}$ radical,

R^{65} and R^{66} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

Z^8 representing a bond, -O-, -NR^{67}- or -S-,

R^{63} and R^{67} representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{64} representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{68}R^{69}$ radical,

R^{68} and R^{69} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;

it being understood that when Het is such that the compound of general formula **(I)** corresponds to general sub-formula $(\mathbf{I})_4$, then:

A represents the 4-hydroxy-2,3-di-tertiobutyl-phenyl radical;

B, R^1 and R^2 all represent H; and finally

Ω represents OH;

or pharmaceutically acceptable salts of the compounds of general formula **(I)**;

can be used for preparing a medicament intended to have at least one of the following three activities:

- to inhibit the monoamine oxydases, in particular monoamine oxydase B,
- to inhibit lipidic peroxidation,
- to have a modulating activity vis-à-vis the sodium channels.

According to preferred variants of the invention, these compounds have at least two of the activities mentioned above. In particular, they inhibit both the MAO's and trap the ROS's or they will have both an antagonist activity vis-à-vis the sodium channels and a trapping activity on the ROS's. In certain cases, the compounds of general formula **(I)** even combine the three activities.

This allows the compounds of general formula (I) to be of use in the treatment of the diseases mentioned previously such as being linked to MAO's, to lipidic peroxidation and to the sodium channels.

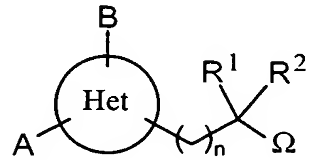
By alkyl, unless otherwise specified, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms. By cycloalkyl, when no further detail is given, is meant a monocyclic carbon system containing 3 to 7 carbon atoms. By alkenyl, when no further detail is given, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one unsaturation (double bond). By alkynyl, when no further detail is given, is meant a linear or branched alkyl radical containing 1 to 6 carbon atoms and having at least one double unsaturation (triple bond). By allenyl, is meant the $-CH=C=CH_2$ radical. By carbocyclic or heterocyclic aryl, is meant a carbocyclic system (in particular, the phenyl radical which can be noted Ph in an abbreviated fashion) or heterocyclic system comprising at least one aromatic ring, a system being called heterocyclic when at least one of the rings which comprises it contains a heteroatom (O, N or S). By heterocycle, is meant a mono- or polycyclic system, said system comprising at least one heteroatom chosen from O, N and S and being saturated, partially or totally unsaturated or aromatic. By heteroaryl, is meant a heterocycle as defined previously in which at least one of the rings which comprises it is aromatic. By haloalkyl, is meant an alkyl radical at least one of hydrogen atoms of which (and optionally all) is replaced by a halogen atom.

Moreover, by an optionally substituted radical is meant unless otherwise specified a radical comprising one or more substituents chosen independently from the group composed of a halogen atom and the alkyl and alkoxy radicals.

By alkylthio, alkoxy, haloalkyl, alkoxyalkyl, trifluoromethylalkyl, cycloalkylalkyl, haloalkoxy, aminoalkyl, alkenyl, alkynyl, allenylalkyl, cyanoalkyl and aralkyl radicals, is meant respectively the alkylthio, alkoxy, haloalkyl, alkoxyalkyl, trifluoromethylalkyl, cycloalkylalkyl, haloalkoxy, aminoalkyl, alkenyl, alkynyl, allenylalkyl, cyanoalkyl and aralkyl radicals the alkyl radical (the alkyl radicals) of which have the meaning(s) indicated previously.

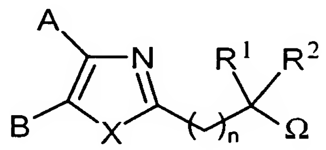
By heterocycle, is meant in particular the thiophene, piperidine, piperazine, quinoline, indoline and indole radicals. By linear or branched alkyl having 1 to 6 carbon atoms, is meant in particular the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl, pentyl, neopentyl, isopentyl, hexyl, isohexyl radicals. Finally, by halogen, is meant the fluorine, chlorine, bromine or iodine atoms.

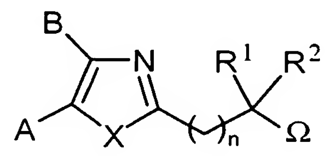
Preferably, the compounds according to the invention are such that they correspond to general formula **(I)**:



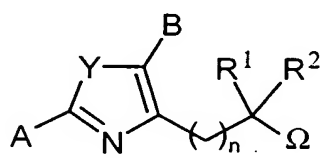
(I)

in racemic, enantiomeric form or any combination of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula **(I)** corresponds exclusively to one of the following sub-formulae:

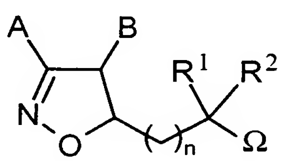




(I)$_1$ **(I)**$_2$



and

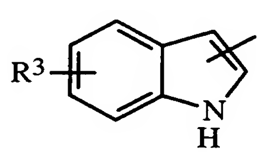


(I)$_3$ **(I)**$_4$

in which

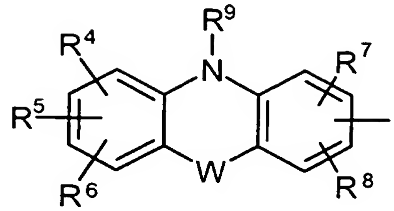
A represents

either a



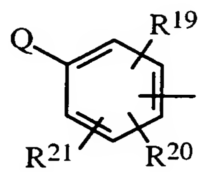
radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or a



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or $NR^{10}R^{11}$ radical,
R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical
R^9 represents a hydrogen atom or an alkyl radical,
and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$, in which R^{18} represents a hydrogen atom or an alkyl radical;

or a



radical in which Q represents H, $-OR^{22}$, $-SR^{22}$, $-NR^{23}R^{24}$, a phenyl radical optionally substituted by one or more substituents chosen independently from a halogen atom, an OH, cyano, nitro, alkyl, alkoxy or $-NR^{10}R^{11}$ radical and a group with two substituents representing together a methylenedioxy or ethylenedioxy radical, or also Q represents a -COPh, -OPh, -SPh, $-SO_2Ph$ or $-CH_2Ph$ radical, said -COPh, -OPh, -SPh, $-SO_2Ph$ or $-CH_2Ph$ radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,
R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^{22} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,
R^{23} and R^{24} representing, independently, a hydrogen atom, an alkyl radical or a $-CO-R^{25}$ radical,
R^{25} representing an alkyl radical,

and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,

R^{26} representing a hydrogen atom or an alkyl radical,

R^{27} and R^{28} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{29}$ group, or R^{27} and R^{28} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,

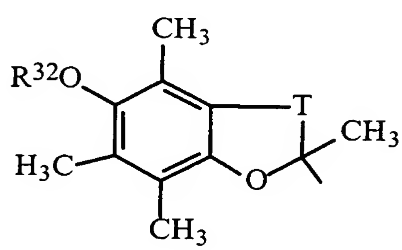
q representing an integer from 0 to 2,

R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

R^{29} representing a hydrogen atom, an alkyl, alkoxy or $-NR^{30}R^{31}$ radical,

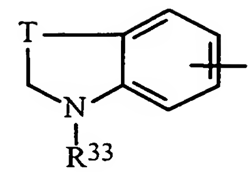
R^{30} and R^{31} representing, independently, a hydrogen atom or an alkyl radical, or R^{30} and R^{31} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical, and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,

Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,

R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals,

R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^{38},

R^{38} representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, $-(CH_2)_g-Z^1R^{39}$, $-(CH_2)_g-COR^{40}$, $-(CH_2)_g-NHCOR^{70}$, aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radical, the aryl group of the aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radicals itself being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^2R^{39}$ or $-(CH_2)_k-COR^{40}$ radicals,

Z^1 and Z^2 representing a bond, -O-, $-NR^{41}-$ or -S-,

R^{39} and R^{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{42}R^{43}$ radical,

R^{42} and R^{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^2 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl or $-(CH_2)_g-NHCOR^{71}$ radical, or also one of the aralkyl or heteroarylalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkoxy, hydroxy, cyano, nitro, amino, alkylamino or dialkylamino radical,

R^{70} and R^{71} representing independently an alkyl or alkoxy radical;

or R^1 and R^2, taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a $-(CH_2)_g-Z^3R^{44}$ radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z^3 representing a bond, -O-, $-NR^{45}-$ or -S-,

R^{44} and R^{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the $NR^{46}R^{47}$ or OR^{48} radicals, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, $-(CH_2)_g-Z^4R^{50}$, $-(CH_2)_k-COR^{51}$, $-(CH_2)_k-COOR^{51}$, $-(CH_2)_k-CONHR^{51}$ or $-SO_2R^{51}$ radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl and in particular pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^5R^{50}$, $-(CH_2)_k-COR^{51}$ and $-(CH_2)_k-COOR^{51}$,

Z^4 and Z^5 representing a bond, -O-, $-NR^{52}-$ or -S-,

or R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S- and -CO-, said heterocycle being able to be for example an azetidine, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine,

R^{50} and R^{52}, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy, allenyl, allenylalkyl or cyanoalkyl radical,

R^{51} representing, independently each time that they occur, a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical has 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, alkoxyalkyl or $NR^{58}R^{59}$ radical, or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical,

R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{53} and R^{54} representing, independently, a hydrogen atom or a $-(CH_2)_k-Z^7R^{60}$ or $-(CH_2)_k-COR^{61}$ radical,

Z^7 representing a bond, -O-, $-NR^{62}-$ or -S-,

R^{60} and R^{62} representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, $-(CH_2)_k-Z^8R^{63}$ and $-(CH_2)_k-COR^{64}$ radicals,

R^{61} representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{65}R^{66}$ radical,

R^{65} and R^{66} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

Z^8 representing a bond, -O-, $-NR^{67}-$ or -S-,

R^{63} and R^{67} representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{64} representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{68}R^{69}$ radical,

R^{68} and R^{69} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;

and R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

it being understood that when Het is such that the compound of general formula **(I)** corresponds to general sub-formula **(I)**$_4$, then:

A exclusively represents the 4-hydroxy-2,3-di-tertiobutyl-phenyl radical;

B represents H,

R^1 and R^2 both represent H; and finally

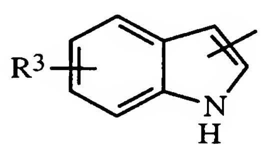
Ω represents OH;

or salts of said compounds

According to the invention, there will generally be preferred the compounds of general formula **(I)** in which at least one of the following radicals is found:

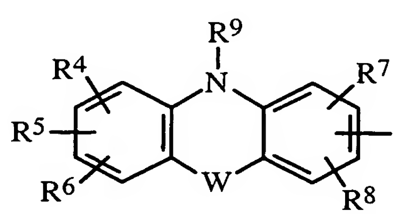
- A representing:

  - either the



radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

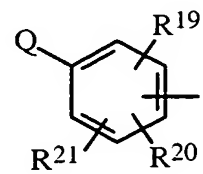
  - or the



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, the OH group or an alkyl or alkoxy radical,

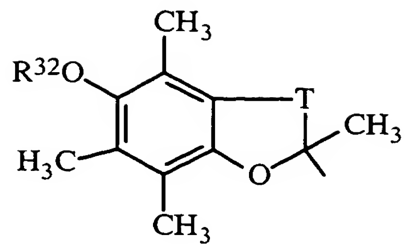
R^9 represents a hydrogen atom or an alkyl radical,
and W does not exist, or represents a bond, -O-, -S- or $-NR^{18}-$, R^{18} representing a hydrogen atom or an alkyl radical;

- or the



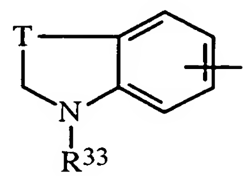
radical in which Q represents H, $-OR^{22}$, $-SR^{22}$ or a phenyl radical optionally substituted by one substituent or substituents chosen independently from a halogen atom, an OH, cyano, nitro, alkyl, alkoxy or $-NR^{10}R^{11}$ radical and a group of two substituents together representing a methylenedioxy or ethylenedioxy radical, or also Q represents an -OPh, -SPh , $-SO_2Ph$ or $-CH_2Ph$ radical, said -OPh, -SPh , $-SO_2Ph$ or $-CH_2Ph$ radical being optionally substituted on its aromatic part by a substituent or substituents chosen from an alkyl or alkoxy radical and a halogen atom,
R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical;
R^{22} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,
and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,
R^{26} representing a hydrogen atom or an alkyl radical,
R^{27} and R^{28} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{29}$ group, or also R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-CH_2-$, -NH- and -O-,
R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,
q representing an integer from 0 to 2,
R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,
R^{29} representing a hydrogen atom, an alkyl, alkoxy or $-NR^{30}R^{31}$ radical,
R^{30} and R^{31} representing, independently, a hydrogen atom or an alkyl radical,

- or the



radical in which R^{32} represents a hydrogen atom or an alkyl radical, and T represents the $-(CH_2)_2-$ radical

- or finally the



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,
Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,
R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,
R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical,
R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

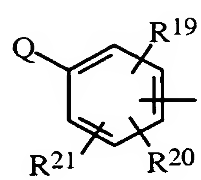
such as for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
and T represents the -(CH_2)- radical;

- Ω representing:

- either the $NR^{46}R^{47}$ radical in which R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, -$(CH_2)_k$-COR^{51}, -$COOR^{51}$ or -SO_2R^{51} radical or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl radicals and in particular pyridinyl, pyridinylalkyl or pyridinylcarbonyl, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by a substituent or substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, -$(CH_2)_k$-Z^5R^{50}, -$(CH_2)_k$-COR^{51} and -$(CH_2)_k$-$COOR^{51}$,
R^{51} representing a hydrogen atom or an alkyl, alkenyl, alkynyl or alkoxyalkyl radical

- or the OH radical;

Moreover, when A represents the



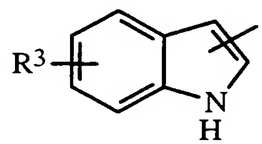
radical, the Q radical is preferably found in para position with respect to the heterocycle Het.

Generally, all the preferences relating to sub-groups of compounds of general formula **(I)** presented below remain applicable with respect to the use of compounds of general formula **(I)** as defined previously for the preparation of medicaments intended to inhibit monoamine oxidases, in particular monoamine oxidase B, to inhibit lipidic peroxidation, to have a modulatory activity on the sodium channels or to have two of the three activities or the three activities mentioned previously.

According to a particular variant of the invention, the compounds of general formula **(I)** or their salts are more especially intended to have an inhibitory activity on MAO's and/or ROS's and they will therefore be preferably such that:

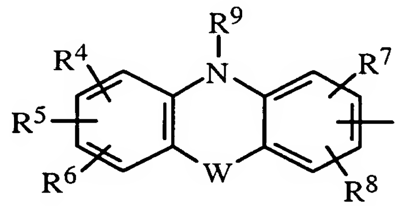
A represents

either a



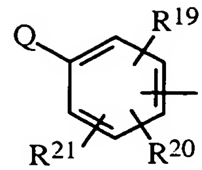
radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or a



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy or $NR^{10}R^{11}$ radical,
R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^9 represents a hydrogen atom or an alkyl radical,
and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$, in which R^{18} represents a hydrogen atom or an alkyl radical;

or a



radical in which Q represents $-OR^{22}$, $-SR^{22}$, $-NR^{23}R^{24}$, a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom and an OH, cyano, nitro, alkyl, alkoxy or $-NR^{10}R^{11}$ radical,

R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

R^{22} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

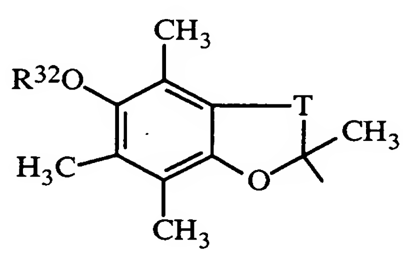
R^{23} and R^{24} representing, independently, a hydrogen atom or an alkyl radical,

and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl, alkenyl, alkoxy or $NR^{27}R^{28}$ radical,

R^{26} representing a hydrogen atom or an alkyl radical,

R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical, or R^{27} and R^{28} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms; said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

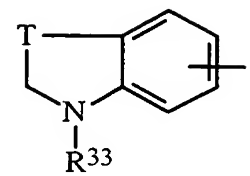
or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical,

and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,

Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,

R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals,

R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

X represents S or NR^{38},

R^{38} representing a hydrogen atom or an alkyl or cyanoalkyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, cycloalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, $-(CH_2)_g-Z^1R^{39}$, $-(CH_2)_g-COR^{40}$, aryl, aralkyl, arylcarbonyl, or aralkylcarbonyl radical, the aryl group of the aryl, aralkyl, arylcarbonyl, or aralkylcarbonyl radicals being itself optionally substituted by a substituent or substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, $-(CH_2)_k-Z^2R^{39}$ or $-(CH_2)_k-COR^{40}$ radicals,

Z^1 and Z^2 representing a bond, -O-, $-NR^{41}-$ or -S-,

R^{39} and R^{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy or cyanoalkyl radical,

R^{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{42}R^{43}$ radical,

R^{42} and R^{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,
and R^2 represents a hydrogen atom or an alkyl radical

B represents a hydrogen atom or a $-(CH_2)_g-Z^3R^{44}$ radical,
Z^3 representing a bond, -O-, $-NR^{45}-$ or -S-,
R^{44} and R^{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the $NR^{46}R^{47}$ or OR^{48} radicals, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, $-(CH_2)_g-Z^4R^{50}$ or $-(CH_2)_k-COR^{51}$ radical. or also a radical chosen from the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^5R^{50}$, $-(CH_2)_k-COR^{51}$ and $-(CH_2)_k-COOR^{51}$,
Z^4 and Z^5 representing a bond, -O-, $-NR^{52}-$ or -S-,
or R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S- and -CO-, said heterocycle being able to be for example an azetidine, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine,
R^{50} and R^{52}, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,
R^{51} representing, independently each time that they occur, a hydrogen atom, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl or $NR^{58}R^{59}$ radical,
R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, alkoxy, allenyl, allenylalkyl or cyanoalkyl radical,
R^{53} and R^{54} representing, independently, a hydrogen atom or a $-(CH_2)_k-Z^7R^{60}$ or $-(CH_2)_k-COR^{61}$ radical,
Z^7 representing a bond, -O-, $-NR^{62}-$ or -S-,
R^{60} and R^{62} representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radical, the aryl or pyridinyl group of the aryl,

aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, $-(CH_2)_k-Z^8R^{63}$ and $-(CH_2)_k-COR^{64}$ radicals,

R^{61} representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{65}R^{66}$ radical,

R^{65} and R^{66} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

Z^8 representing a bond, -O-, $-NR^{67}-$ or -S-,

R^{63} and R^{67} representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{64} representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{68}R^{69}$ radical,

R^{68} and R^{69} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

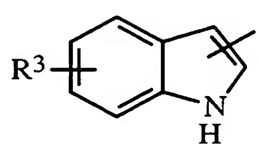
and R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6.

More preferentially, the compounds of general formula **(I)** (or their salts), when they are intended to have an inhibitory activity on MAO's and/or ROS's, will be such that:

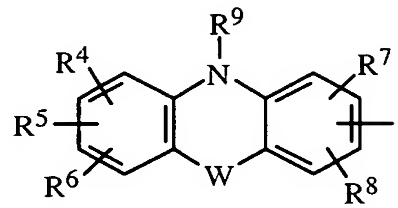
A represents

either a



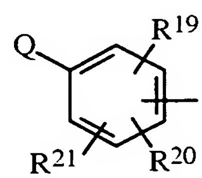
radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or a



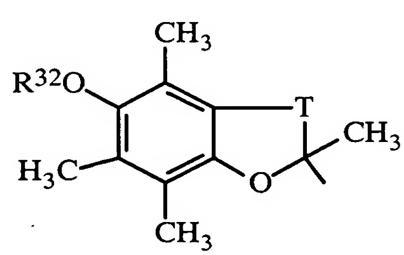
radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, or an alkyl or alkoxy radical,
R^9 represents a hydrogen atom,
and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$, in which R^{18} represents a hydrogen atom or an alkyl radical;

or a



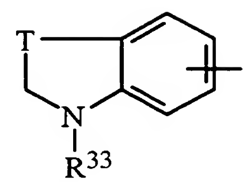
radical in which Q represents $-OR^{22}$, $-SR^{22}$ or a phenyl radical substituted by an OH radical and optionally one or more of the additional substituents chosen independently from a halogen atom and an OH, alkyl or alkoxy radical,
R^{22} representing a hydrogen atom or an alkyl radical,
and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl or alkoxy radical,
R^{26} representing a hydrogen atom or an alkyl radical,

or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical,
and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,

Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,

R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,

R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro or alkoxy radicals,

and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

X represents S or NR^{38},

R^{38} representing a hydrogen atom or an alkyl or cyanoalkyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, cycloalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, $-(CH_2)_g-Z^1R^{39}$, $-(CH_2)_g-COR^{40}$, aryl, aralkyl, arylcarbonyl, or aralkylcarbonyl radical, the aryl group of the aryl, aralkyl, arylcarbonyl, or aralkylcarbonyl radicals being itself optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, $-(CH_2)_k-Z^2R^{39}$ or $-(CH_2)_k-COR^{40}$ radicals,

Z^1 and Z^2 representing a bond, -O-, $-NR^{41}-$ or -S-,

R^{39} and R^{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{42}R^{43}$ radical,

R^{42} and R^{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^2 represents a hydrogen atom or an alkyl radical

B represents a hydrogen atom or a $-(CH_2)_g-Z^3R^{44}$ radical,

Z^3 representing a bond, -O-, $-NR^{45}-$ or -S-,

R^{44} and R^{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the $NR^{46}R^{47}$ or OR^{48} radicals, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, $-(CH_2)_g-Z^4R^{50}$ or $-(CH_2)_k-COR^{51}$ radical, or also a radical chosen from the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^5R^{50}$, $-(CH_2)_k-COR^{51}$ and $-(CH_2)_k-COOR^{51}$,

Z^4 and Z^5 representing a bond, -O-, $-NR^{52}-$ or -S-,

or R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group comprising $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S- and -CO-, said heterocycle being able to be for example an azetidine, a piperazine, a homopiperazine, a 3,5-dioxopiperazine, a piperidine, a pyrrolidine, a morpholine or a thiomorpholine,

R^{50} and R^{52}, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{51} representing, independently each time that they occur, a hydrogen atom, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl or $NR^{58}R^{59}$ radical,

R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{53} and R^{54} representing, independently, a hydrogen atom or a $-(CH_2)_k-Z^7R^{60}$ or $-(CH_2)_k-COR^{61}$ radical,

Z^7 representing a bond, -O-, $-NR^{62}-$ or -S-,

R^{60} and R^{62} representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, $-(CH_2)_k-Z^8R^{63}$ and $-(CH_2)_k-COR^{64}$ radicals,

R^{61} representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{65}R^{66}$ radical,

R^{65} and R^{66} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

Z^8 representing a bond, -O-, $-NR^{67}-$ or -S-,

R^{63} and R^{67} representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,
R^{64} representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{68}R^{69}$ radical,
R^{68} and R^{69} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

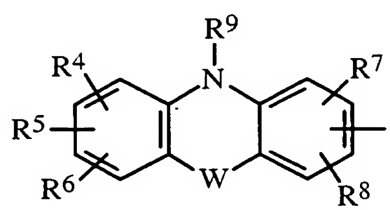
g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6.

As regards the compounds of general formula **(I)** (or their salts) more especially intended to have an inhibitory activity on MAO's and the ROS's, the said compounds compounds having at least one of the following characteristics will generally be preferred:

- the compound corresponds to general sub-formula $\mathbf{(I)}_1$ or $\mathbf{(I)}_2$ in which X represents S, the compounds corresponds to general formula $\mathbf{(I)}_3$ in which Y represents O or the compound corresponds to general sub-formula $\mathbf{(I)}_4$;

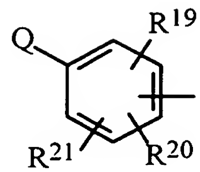
- A represents the radical

  - either the



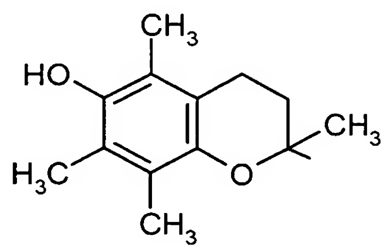
radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, or an alkyl or alkoxy radical,
R^9 represents a hydrogen atom,
and W doesn't exist, or represents a bond, -O- or -S-,

  - or the



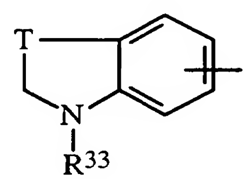
radical in which Q represents OH, two of the R^{19}, R^{20} and R^{21} radicals represent the radicals chosen independently from the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals and the third represents a radical chosen from a hydrogen atom and the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals, or in which Q represents a phenyl radical substituted by an OH radical and a radical or radicals chosen independently from a halogen atom and an OH, alkyl, alkoxy or $-NR^{10}R^{11}$ radical in which R^{10} and R^{11} represent independently a hydrogen atom or an alkyl radical,

- or also the



radical

- or finally the



radical in which T represents $-CH_2-$ and R^{33} represents a hydrogen atom, an aminoalkyl, alkylaminoalkyl or dialkylaminoalkyl radical;

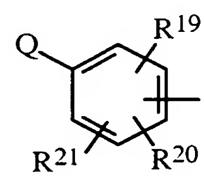
- B represents H;
- n represents 0 or 1;
- R^1 and R^2 both represent H;
- Ω represents

- preferably: an $NR^{46}R^{47}$ radical such that $NR^{46}R^{47}$ represents the N-piperazinyl radical or the N-piperazinyl radical optionally N-substituted by an alkyl radical or in which one of R^{46} and R^{47} represents H or a hydroxyalkyl, alkynyl or cyanoalkyl radical and the other represents H or an alkyl radical.

- or the OR^{48} radical in which R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical.

As regards the compounds of general formula **(I)** (or their salts) more especially intended to have an inhibitory activity on MAO's and the ROS's, the said compounds having at least one of the following characteristics will be quite particularly preferred:

- the compound corresponds to general sub-formula $\mathbf{(I)_1}$ or $\mathbf{(I)_2}$ in which X represents S or the compound corresponds to general formula $\mathbf{(I)_3}$ in which Y represents O;
- A represents the



radical in which Q represents OH, two of the R^{19}, R^{20} and R^{21} radicals represent an alkyl radical and the third represents H,
or in which Q represents a phenyl radical substituted by an OH radical and one or more radicals chosen independently from the alkyl radicals;

- B represents H;
- n represents 0 or 1;
- R^1 and R^2 both represent H;
- Ω represents:

- preferably: an $NR^{46}R^{47}$ radical such that $NR^{46}R^{47}$ represents an N-piperazinyl radical or in which one of R^{46} and R^{47} represents H or a hydroxyalkyl, alkynyl or cyanoalkyl radical and the other represents H or an alkyl radical,

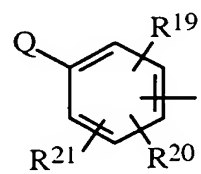
- or the OH radical.

In particular, the compounds of Examples 1 to 30, 210, 291, 316, 319 to 323, 329 to 336 and 346 to 349 (sometimes described in the form of salts) or their pharmaceutically acceptable salts are preferred when an inhibitory activity on MAO's and/or the ROS's is sought in the first place. Even more preferentially, the compounds of Examples 1, 3, 6, 22, 24, 26 to 29, 323 and 332 (sometimes described in the form of salts), or their pharmaceutically acceptable salts, are preferred when an inhibitory activity on MAO's and/or the ROS's is sought in the first place.

According to another variant of the invention, the compounds of general formula **(I)** or their pharmaceutically acceptable salts are more especially intended to have an modulating activity on the sodium channels and they are then preferably such that they correspond to general sub-formulae $\mathbf{(I)}_1$ and $\mathbf{(I)}_2$ and that:

A represents

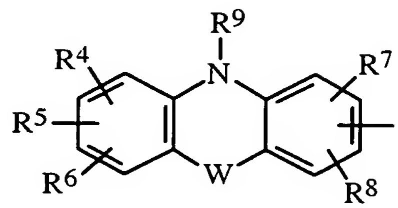
either a



radical in which Q represents H, $-OR^{22}$, SR^{22} or a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom, an alkyl or alkoxy radical, and a group of two substituents together representing a methylenedioxy or ethylenedioxy radical, or Q represents a -COPh, -OPh, -SPh , $-SO_2Ph$ or $-CH_2Ph$ radical, said -COPh, -OPh, -SPh , $-SO_2Ph$ or $-CH_2Ph$ radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,
R^{22} representing a hydrogen atom or an alkyl radical,
and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro, cycloalkyl, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,
R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical or R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-CH_2-$, -NH- and -O-,
R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,
q representing an integer from 0 to 2,

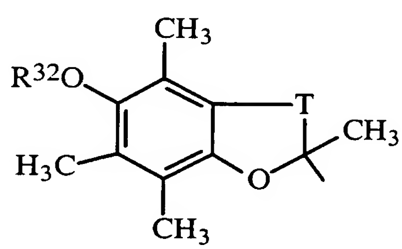
R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

or a



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy or $NR^{10}R^{11}$ radical,
R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle comprising 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,
R^9 represents a hydrogen atom or an alkyl radical,
and W does not exist, or represents a bond, or -O-, -S- or -NR^{18}-, in which R^{18} represents a hydrogen atom or an alkyl radical;

or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical,
and T represents a -$(CH_2)_m$- radical with m = 1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

B represents a hydrogen atom, a linear or branched alkyl radical containing 1 to 6 carbon atoms or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, an alkyl or alkoxy radical,

a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical;

X represents NR^{38} or S,
R^{38} representing a hydrogen atom or an alkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

R^1 and R^2 represent, independently, a hydrogen atom, an alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aminoalkyl, $-(CH_2)_g-NH-CO-R^{70}$ radical or an aralkyl or heteroarylalkyl radical optionally substituted on the aryl or heteroaryl group by one or more groups chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical and an amino, alkylamino or dialkylamino radical,
R^{70} representing, independently each time that it occurs, an alkyl or alkoxy radical;

R^1 and R^2 taken together can optionally form with the carbon atom which carries them a carbocycle with 3 to 7 members;

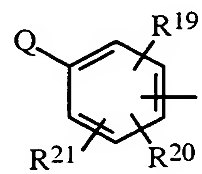
Ω represents OH or an $NR^{46}R^{47}$ radical, in which:
R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl or cycloalkylalkyl, $-CO-NH-R^{51}$, $-CO-O-R^{51}$ or $-SO_2-R^{72}$ radical or one of the heteroaryl, aralkyl, aryloxyalkyl or arylimino radicals optionally substituted on the heteroaryl or aryl group by one or more groups chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical,
R^{51} representing a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical contains 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkoxyalkyl radical or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical,
and R^{72} representing an alkyl radical, or one of the phenyl or aralkyl radicals optionally substituted on the aromatic ring by one or more of the radicals chosen from a halogen atom, an alkyl or alkoxy radical;

g represents an integer from 1 to 6; and finally

n represents an integer from 0 to 6.

More preferentially, the compounds of general formula **(I)** (or their pharmaceutically acceptable salts) intended to have a modulating activity on the sodium channels corresponding to general sub-formulae **(I)**$_1$ and **(I)**$_2$ and will be such that:

A represents the



radical in which Q represents H, -OR^{22}, -SR^{22} or a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical, or also Q represents a -COPh, -OPh, -SPh , -SO$_2$Ph or –CH$_2$Ph radical, said -COPh, -OPh, -SPh , -SO$_2$Ph or –CH$_2$Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen from an alkyl or alkoxy radical and a halogen atom,
R^{22} representing a hydrogen atom or an alkyl radical,
and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro, cycloalkyl, -SO$_2$NHR^{49}, -CONHR^{55}, -S(O)$_q$R^{56}, -NH(CO)R^{57}, -OCF$_3$ or NR^{27}R^{28} radical,
R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical or R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from -CH$_2$-, -NH- and -O-,
R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,
q representing an integer from 0 to 2,
R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical,

B represents a hydrogen atom, a linear or branched alkyl radical containing 1 to 6 carbon atoms or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical;

X represents NR^{38} or S,

R^{38} representing a hydrogen atom or an alkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

R^1 and R^2 represent, independently, a hydrogen atom, an alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, aminoalkyl, $-(CH_2)_g-NH-CO-R^{70}$ radical or an aralkyl or heteroarylalkyl radical optionally substituted on the aryl or heteroaryl group by one or more groups chosen from the group composed of a halogen atom, an alkyl or alkoxy radical, a hydroxy, cyano or nitro radical and an amino, alkylamino or dialkylamino radical,

R^{70} representing, independently each time that it occurs, an alkyl or alkoxy radical;

R^1 and R^2 taken together can optionally form with the carbon atom which carries them a carbocycle with 3 to 7 members;

Ω represents the $NR^{46}R^{47}$ radical, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl or cycloalkylalkyl, $-CO-NH-R^{51}$, $-CO-O-R^{51}$ or $-SO_2-R^{72}$ radical or one of the heteroaryl, aralkyl, aryloxyalkyl or arylimino radicals optionally substituted on the heteroaryl or aryl group by one or more groups chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical,

R^{51} representing a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical contains 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkoxyalkyl radical or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical,

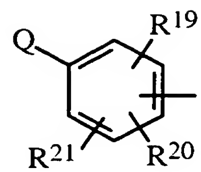
and R^{72} representing an alkyl radical, or one of the phenyl or aralkyl radicals optionally substituted on the aromatic ring by one or more of the radicals chosen from a halogen atom, an alkyl or alkoxy radical and finally;

n represents an integer from 0 to 6.

As regards the compounds of general formula **(I)** (or their salts) more especially intended to have a modulating activity on the sodium channels, said compounds of general sub-formula $\mathbf{(I)_1}$ or $\mathbf{(I)_2}$ will generally be preferred having at least one of the following characteristics:

- A represents:

  - the



radical in which Q represents a hydrogen atom, a halogen atom, the OH group, an alkoxy, alkylthio or phenyl radical optionally substituted by one or more radicals chosen from a halogen atom and an alkoxy radical,
and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen atom, a halogen atom, the OH group or an alkyl, alkoxy, cyano, nitro, cycloalkyl, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,
R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical or R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-CH_2-$, -NH- and -O-,
R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,
q representing an integer from 0 to 2,
R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical;

  - or an alkyl, cycloalkyl or cycloalkylalkyl radical;

- B represents H, alkyl, or phenyl;

- n represents 0 or 1;

- R^1 and R^2 are such that:

  - R^1 and R^2 represent independently H, an alkyl, cycloalkyl radical and in particular cyclohexyl, cycloalkylalkyl, or also an aralkyl or heteroarylalkyl radical optionally substituted on the aryl or heteroaryl group by one or more groups chosen from the group comprising a halogen atom, an alkyl or alkoxy radical; in particular, R^1 represents a linear or branched alkyl radical containing 2 to 6 carbon atoms, and preferably 4 to 6 carbon atoms, the cyclohexyl radical or the indolylmethyl radical optionally substituted and R^2 represents H;

- or R^1 and R^2 taken together with the carbon atom which carries them a carbocycle with 3 to 7 members;

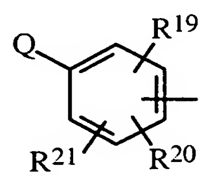
- Ω represents an OH radical or preferably an $NR^{46}R^{47}$ radical in which R^{46} represents H, an alkyl radical and in particular isopropyl, n-pentyl or n-hexyl, a cycloalkylalkyl radical, a cycloalkyl radical and in particular cyclobutyl, cyclopentyl or cyclohexyl, an alkylcarbonyl radical, an alkoxycarbonyl radical, a (cycloalkyl)oxycarbonyl radical, a cycloalkylalkoxycarbonyl radical, an alkylaminocarbonyl radical or also a benzyl radical optionally substituted by an alkoxy radical, and R^{47} represents H;

- X represents S or preferably the NR^{38} radical in which R^{38} represents a hydrogen atom or an alkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical.

As regards the compounds of general formula **(I)** (or their salts) more particularly intended to have a modulatory activity on the sodium channels, said compounds of general sub-formula $\mathbf{(I)}_1$ or $\mathbf{(I)}_2$ comprising at least one of the following characteristics will be even more particularly preferred:

- A represents:

  - the



radical in which Q represents a hydrogen atom, a halogen atom or an alkoxy, alkylthio or phenyl radical optionally substituted by one or more radicals chosen from a halogen atom and an alkoxy radical,
and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen atom, a halogen atom or an alkyl, alkoxy, cyano, cycloalkyl, $-CF_3$ or $NR^{27}R^{28}$ radical,
R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical or R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-CH_2-$ and -NH- ;

  - or a cycloalkyl radical;

- B represents H;

- n represents 0 or 1;

- R^1 represents H, an alkyl, cycloalkyl and in particular a cyclohexyl radical, and R^2 represents H;

- Ω represents an $NR^{46}R^{47}$ radical in which R^{46} represents a cycloalkylalkyl radical, a cycloalkyl radical and in particular cyclobutyl or cyclohexyl, an alkoxycarbonyl radical, a (cycloalkyl)oxycarbonyl radical, a cycloalkylalkoxycarbonyl radical or also a benzyl radical optionally substituted by an alkoxy radical, and R^{47} represents H;

- X represents the NH radical.

Furthermore, still for the compounds more particularly intended to have a modulatory activity on sodium channels, when n represents 1, R^1 and R^2 will preferably represent hydrogen atoms.

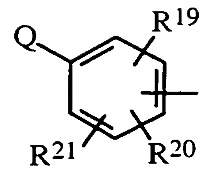
In particular, the compounds of Examples 1, 3, 6, 7, 9 to 11, 13, 15 to 17, 20, 24, 26, 28 to 318, 321, 324 to 330 and 337 to 345 (sometimes described in the form of salts), or their pharmaceutically acceptable salts, are preferred when a modulating activity on the sodium channels is sought in the first place.

More preferentially, the compounds of Examples 1, 6, 7, 11, 13, 15, 17, 20, 24, 31 to 38, 42, 43, 46 to 48, 53, 56, 57, 59 to 61, 64 to 80, 82 to 88, 92 to 95, 97, 105, 106, 108, 110, 113, 117, 118, 121 to 123, 125, 128, 130 to 139, 142 to 145, 149, 151, 152, 154, 162 to 166, 168 to 178, 181, 183 to 186, 188, 190 to 196, 198 to 206, 208 to 210, 212 to 218, 220 to 231, 233 to 250, 252 to 259, 261 to 281, 283 to 288, 293 to 313, 324 and 338 to 340 (sometimes described in the form of salts), or their pharmaceutically acceptable salts, are preferred when a modulating activity on the sodium channels is sought in the first place.

According to a more particular variant of the invention, the compounds of the invention of general formula **(I)** as defined previously in which:

Het is such that the compounds of general formula **(I)** correspond to one of the general sub-formulae $\mathbf{(I)}_1$ and $\mathbf{(I)}_2$ in which X represents NH or S or general sub-formula $\mathbf{(I)}_3$ in which Y represents O;

A represents a



radical in which Q represents OH, two of the R^{19}, R^{20} and R^{21} radicals represent an alkyl radical and the third represents a hydrogen atom,
or in which Q represents a phenyl radical substituted by an OH radical and one or more radicals chosen independently from alkyl radicals;

B represents a hydrogen atom;

n represents 0 or 1;

R^1 and R^2 both represent a hydrogen atom;

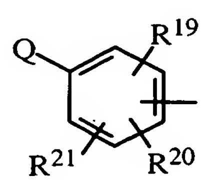
and Ω represents an $NR^{46}R^{47}$ radical in which R^{46} represents a hydrogen atom or an alkyl, alkynyl, hydroxyalkyl or cyanoalkyl radical and R^{47} represents a hydrogen atom or an alkyl radical or also R^{46} and R^{47} form together with the nitrogen atom which carries them a non-aromatic heterocycle with 5 to 7 members, the additional members being chosen from $-CH_2-$ and -NH-;

can be used to prepare a medicament intended both to inhibit MAO's and lipidic peroxidation and to modulate the sodium channels.

More preferentially, the compounds of general formula **(I)** which can be used to prepare a medicament intended both to inhibit MAO's and lipidic peroxidation and to modulate the sodium channels will be such that:

Het is such that the compounds of general formula **(I)** correspond to general sub-formula **(I)**$_1$ in which X represents S or to general sub-formula **(I)**$_3$ in which Y represents O;

A represents a



radical in which Q represents OH, two of the radicals R^{19}, R^{20} and R^{21} represent an alkyl radical and the third represents a hydrogen atom;

B represents a hydrogen atom;

n represents 0 or 1;

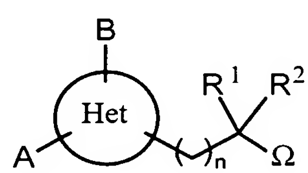
R^1 and R^2 both represent a hydrogen atom;

and Ω represents an $NR^{46}R^{47}$ radical in which R^{46} represents a hydrogen atom or an alkyl, hydroxyalkyl or cyanoalkyl radical and R^{47} represents a hydrogen atom or an alkyl radical or also R^{46} and R^{47} form together with the nitrogen atom which carries them an N-piperazinyl radical.

Still for the compounds of general formula **(I)** which can be used to prepare a medicament intended both to inhibit the MAO's and lipidic peroxidation and to modulate the sodium channels, n will preferably represent 0 when Het is such that the compounds of general formula **(I)** correspond to general sub-formula **(I)**$_1$ in which X represents S and preferably 1 when Het is such that the compounds of general formula **(I)** correspond to general sub-formula **(I)**$_3$ in which Y represents O.

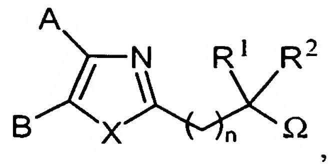
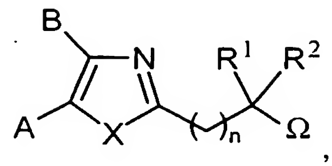
In particular, the compounds of Examples 1, 3, 6, 24, 26, 28 and 29 (sometimes described in the form of salts) or their pharmaceutically acceptable salts will be preferred if one wishes to prepare a medicament intended both to inhibit MAO's and lipidic peroxidation and to modulate the sodium channels.

The invention also offers, as medicaments, the compounds of general formula **(II)**

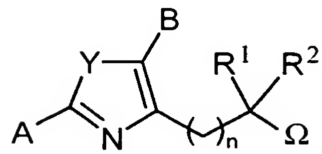
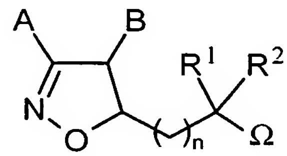


(II)

in racemic, enantiomeric form or any combinations of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula **(II)** correspond exclusively to one of the following sub-formulae:

(II)$_1$ (II)$_2$

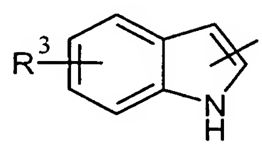

and


(II)$_3$ (II)$_4$

in which

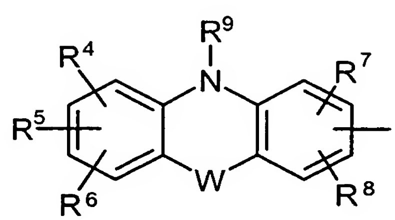
A represents

either a



radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or a



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or $NR^{10}R^{11}$ radical,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a -COR^{12} group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical, R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

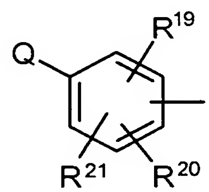
R^9 represents a hydrogen atom, an alkyl radical or a $-COR^{15}$ group,

R^{15} representing a hydrogen atom or an alkyl, alkoxy or $NR^{16}R^{17}$radical,

R^{16} and R^{17} representing, independently, a hydrogen atom or an alkyl radical, or R^{16} and R^{17} forming together with the nitrogen atom an optionally substituted heteroatom with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$, in which R^{18} represents a hydrogen atom or an alkyl radical;

or a



radical in which Q represents H, $-OR^{22}$, $-SR^{22}$, $-NR^{23}R^{24}$, a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom, an OH, cyano, nitro, alkyl, alkoxy or $-NR^{10}R^{11}$ radical and a group with two substituents together representing a methylenedioxy or ethylenedioxy radical, or also Q represents a -COPh, $-SO_2Ph$ or $-CH_2Ph$ radical, said -COPh, $-SO_2Ph$ or $-CH_2Ph$ radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,

R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{12} representing a hydrogen atom, an alkyl or alkoxy or $NR^{13}R^{14}$ radical,

R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{22} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

R^{23} and R^{24} representing, independently, a hydrogen atom, an alkyl radical or a -CO-R^{25} radical,

R^{25} representing an alkyl radical,

and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,

R^{26} representing a hydrogen atom or an alkyl radical,

R^{27} and R^{28} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{29}$ group, or R^{27} and R^{28} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,

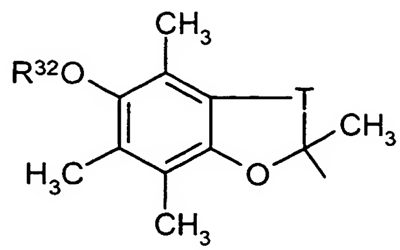
q representing an integer from 0 to 2,

R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

R^{29} representing a hydrogen atom, an alkyl, alkoxy or $-NR^{30}R^{31}$ radical,

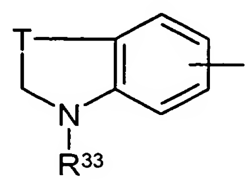
R^{30} and R^{31} representing, independently, a hydrogen atom or an alkyl radical, or R^{30} and R^{31} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical, and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,
Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,
R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,
R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical,
R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^{38},

R^{38} representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, $-(CH_2)_g-Z^1R^{39}$, $-(CH_2)_g-COR^{40}$, $-(CH_2)_g-NHCOR^{70}$, aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radical, the aryl group of the aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radicals being itself optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^2R^{39}$ or $-(CH_2)_k-COR^{40}$ radicals,

Z^1 and Z^2 representing a bond, -O-, $-NR^{41}-$ or -S-,

R^{39} and R^{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{42}R^{43}$ radical,

R^{42} and R^{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^2 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl or $-(CH_2)_g-NHCOR^{71}$ radical, or also one of the aralkyl or heteroarylalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkoxy, hydroxy, cyano, nitro, amino, alkylamino or dialkylamino radical,

R^{70} and R^{71} representing independently an alkyl or alkoxy radical;

or R^1 and R^2, taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a $-(CH_2)_g-Z^3R^{44}$ radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z^3 representing a bond, -O-, $-NR^{45}-$ or -S-,

R^{44} and R^{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the $NR^{46}R^{47}$ or OR^{48} radicals, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, $-(CH_2)_g-Z^4R^{50}$, $-(CH_2)_k-COR^{51}$, $-(CH_2)_k-COOR^{51}$, $-(CH_2)_k-CONHR^{51}$ or $-SO_2R^{51}$ radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl and in particular pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^5R^{50}$, $-(CH_2)_k-COR^{51}$ and $-(CH_2)_k-COOR^{51}$,

Z^4 and Z^5 representing a bond, -O-, $-NR^{52}-$ or -S-,

or R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S- and -CO-,

R^{50} and R^{52}, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{51} representing, independently each time that they occur, a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical contains 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, alkoxyalkyl or $NR^{58}R^{59}$ radical, or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more of the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical,

R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{53} and R^{54} representing, independently, a hydrogen atom or a $-(CH_2)_k-Z^7R^{60}$ or $-(CH_2)_k-COR^{61}$ radical,

Z^7 representing a bond, -O-, $-NR^{62}-$ or -S-,

R^{60} and R^{62} representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, $-(CH_2)_k-Z^8R^{63}$ and $-(CH_2)_k-COR^{64}$ radicals,

R^{61} representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{65}R^{66}$ radical,

R^{65} and R^{66} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

Z^8 representing a bond, -O-, -NR^{67}- or -S-,

R^{63} and R^{67} representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical

R^{64} representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{68}R^{69}$ radical,

R^{68} and R^{69} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;

it being understood that when Het is such that the compound of general formula **(II)** corresponds to general sub-formula $\mathbf{(II)}_4$, then:

A represents the 4-hydroxy-2,3-di-tertiobutyl-phenyl radical;

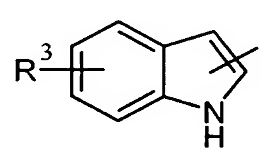
B, R^1 and R^2 all represent H; and finally

Ω represents OH;

it also being understood that at least one of the following characteristics must be present:

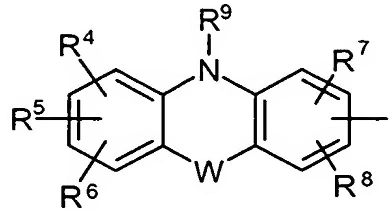
- Het is a thiazole, oxazole or isoxazoline ring, and

A represents a



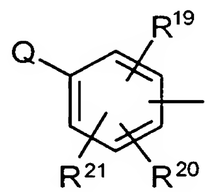
radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or A represents a



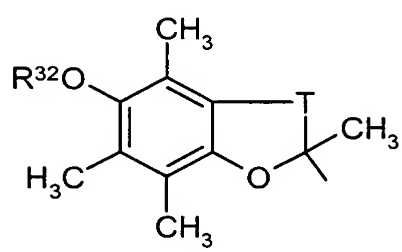
radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or $NR^{10}R^{11}$ radical, R^{10} and R^{11} representing, independently, a hydrogen atom or an alkyl radical
R^9 represents a hydrogen atom or an alkyl radical,
and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$, in which R^{18} represents a hydrogen atom or an alkyl radical,

or A represents a



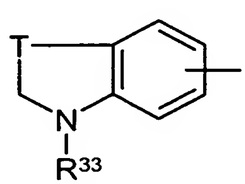
radical in which Q represents OH or Q represents a phenyl radical substituted by an OH radical and one or more of the radicals chosen independently from a halogen atom and an OH, alkyl, alkoxy or $-NR^{10}R^{11}$ radical in which R^{10} and R^{11} represent independently a hydrogen atom or an alkyl radical,

or also A represents a



radical in which R^{32} represents a hydrogen atom or an alkyl radical and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally A represents a

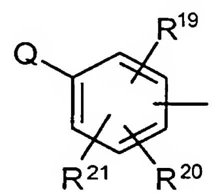


radical in which the R^{33} radical represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical, Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms, R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical, R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals, R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms, said heterocycle being able to be for example azetidine, pyrrolidine, piperidine, piperazine, morpholine or thiomorpholine,

and T represents a $-(CH_2)_m-$ radical with m = 1 or 2;

- Het is an imidazole ring,

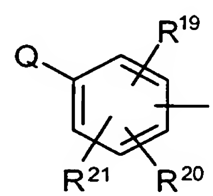
  A represents a



  radical in which Q represents OH,

  and Ω represents $NR^{46}R^{47}$ in which R^{46} or R^{47} represents an aminophenyl, nitrophenyl, aminophenylcarbonyl, nitrophenylcarbonyl, aminophenylalkyl or nitrophenylalkyl radical;

- A represents a



  radical B represents a carbocyclic aryl radical optionally substituted 1 to 3 times by radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

and one of R^1 and R^2 represents one of the optionally substituted arylalkyl or heteroarylalkyl radicals;

- A represents a cycloalkyl or cycloalkylalkyl radical;

- Ω represents $NR^{46}R^{47}$ and one of R^{46} and R^{47} represents an alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl or hydroxyalkyl radical;

- one of R^1 and R^2 represents a cycloalkyl or cycloalkylalkyl radical;

- none of R^1 and R^2 represents H;

- n = 1 and A represents a biphenyl, phenoxyphenyl, phenylthiophenyl, phenylcarbonylphenyl or phenylsulphonylphenyl radical;

- when Het is a thiazole ring and Ω represents the OR^{48} radical in which R^{48} is a cyanoalkyl radical, then the cyano group is not attached to the carbon atom immediately adjacent to the oxygen atom;

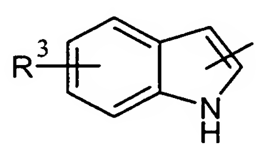
or the pharmaceutically acceptable salts of the compounds of general formula **(II)**.

Generally, the medicaments of general formula **(II)** having one of the following additional characteristics are preferred:

i. n = 0,

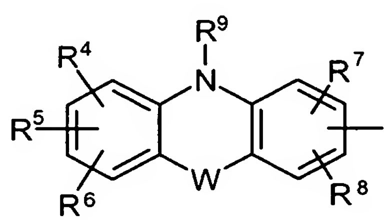
Het is an oxazole, thiazole or isoxazoline ring

A represents a



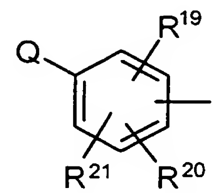
radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or A represents a



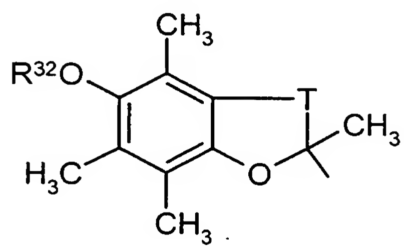
radical in which R^4, R^5, R^6, R^7, R^8 and R^9 represent hydrogen atoms and W doesn't exist, or represents a bond, or -O-, -S- or $-NR^{18}-$ in which R^{18} represents a hydrogen atom or an alkyl radical,

or A represents a



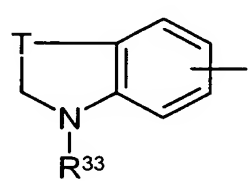
radical in which Q represents OH and two of the R^{19}, R^{20} and R^{21} radicals represent alkyl radicals,
or in which Q represents a phenyl radical substituted by an OH radical and a radical or radicals chosen independently from a halogen atom and an OH, alkyl, alkoxy or $-NR^{10}R^{11}$ radical in which R^{10} and R^{11} represent independently a hydrogen atom or an alkyl radical,

or also A represents a



radical in which R^{32} represents a hydrogen atom or an alkyl radical and T represents $-(CH_2)_2-$,

or finally A represents a



radical in which T represents the $-CH_2-$ radical and the R^{33} radical represents a hydrogen atom or a $-\Sigma-NR^{34}R^{35}$ radical, Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms, and R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,

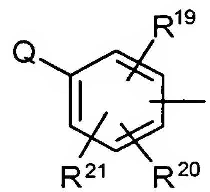
B represents H,

R^1 and R^2 represent, independently, a hydrogen atom or an alkyl radical,

and Ω represents an $NR^{46}R^{47}$ radical in which one of R^{46} and R^{47} represents an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl or hydroxyalkyl radical and the other represents a hydrogen atom or an alkyl radical; or

ii. n = 0,

A represents a



radical in which Q represents a hydrogen atom or an $-OR^{22}$ or $-SR^{22}$ radical in which R^{22} represents an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,
R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, an SR^{26} radical, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,
R^{26} representing an alkyl radical,
R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical or R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-CH_2-$, -NH- and -O-,
R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,
q representing an integer from 0 to 2,
R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

and one of R^1 and R^2 represents a cycloalkyl or cycloalkylalkyl radical or none of R^1 and R^2 represent a hydrogen atom; or finally

iii. n = 1,

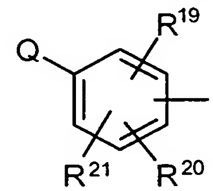
A represents an optionally substituted biphenyl radical or the cyclohexylphenyl radical,

B represents a hydrogen atom,

R^1 and R^2 each represent a hydrogen atom,

and Ω represents an $NR^{46}R^{47}$ radical in which R^{46} represents a $-COOR^{51}$ radical, R^{51} representing an alkyl, cycloalkyl, cycloalkylalkyl or alkoxyalkyl radical and R^{47} representing a hydrogen atom.

In case i., it is preferred moreover that A represents a



radical in which Q represents OH and two of the R^{19}, R^{20} and R^{21} radicals represent alkyl radicals.

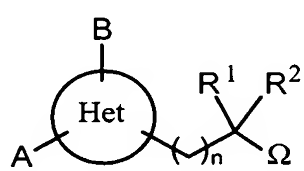
In cases ii. and iii., it is preferred moreover that Het represents an imidazole ring.

Preferably, the medicaments of general formula **(II)** will be chosen from the compounds described (sometimes in the form of salts) in Examples 1 to 35, 52, 57, 61, 80, 82, 83, 85 to 87, 90, 94, 113, 115, 123, 127, 130, 132, 134, 138, 139, 147, 152, 154, 161, 164, 169, 171 to 173, 176 to 180, 203, 237 to 239, 243 to 247, 249, 251, 255, 258 to 262, 264 to 271, 273 to 275 and 277 to 349, or the pharmaceutically acceptable salts of these compounds.

More preferentially, the medicaments of general formula **(II)** will be chosen from the compounds described (sometimes in the form of salts) in Examples 1, 3, 6, 7, 11, 17, 24, 26 to 35, 57, 61, 82, 83, 85 to 87, 94, 113, 123, 130, 132, 134, 138, 139, 152, 154, 164, 169, 171 to 173, 176 to 178, 203, 237 to 239, 243 to 247, 249, 255, 258, 259, 261, 262, 264 to 271, 273 to 275, 277 to 281, 283 to 288, 293 to 313, 321, 323, 324, 332 and 338 to 340, or the pharmaceutically acceptable salts of these compounds.

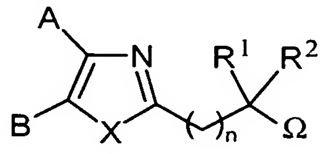
Moreover, the same preferences as those indicated for the compounds of general formula **(I)** are moreover applicable by analogy to the compounds of general formula **(II)**.

The invention also relates, as new industrial products, to the compounds of general formula **(III)**

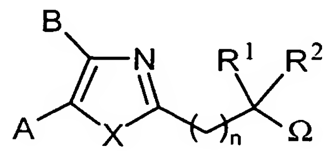


(III)

in racemic, enantiomeric form or any combinations of these forms, in which Het is a heterocycle with 5 members comprising 2 heteroatoms and such that general formula **(III)** corresponds exclusively to one of the following sub-formulae:

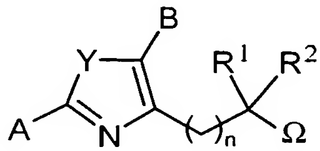


,

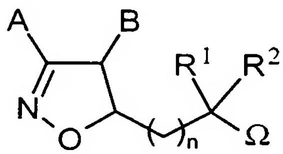


,

(III)$_1$ **(III)$_2$**



and

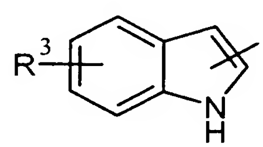


(III)$_3$ **(III)$_4$**

in which

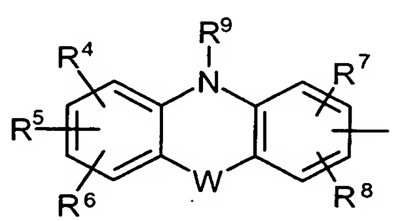
A represents

either a



radical in which R^3 represents a hydrogen atom, the OH group or an alkoxy or alkyl radical,

or a



radical in which R^4, R^5, R^6, R^7 and R^8 represent, independently, a hydrogen atom, a halogen, the OH group or an alkyl, alkoxy, cyano, nitro or $NR^{10}R^{11}$ radical,

R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a -COR^{12} group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical,

R^{13} and R^{14} represent, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

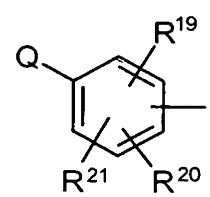
R^9 represents a hydrogen atom, an alkyl radical or a -COR^{15} group,

R^{15} representing a hydrogen atom or an alkyl, alkoxy or $NR^{16}R^{17}$ radical,

R^{16} and R^{17} representing, independently, a hydrogen atom or an alkyl radical, or R^{16} and R^{17} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

and W doesn't exist, or represents a bond, or -O-, -S- or -NR^{18}-, in which R^{18} represents a hydrogen atom or an alkyl radical;

or a



radical in which Q represents H, -OR^{22}, -SR^{22}, -$NR^{23}R^{24}$, a phenyl radical optionally substituted by one or more of the substituents chosen independently from a halogen atom, an OH, cyano, nitro, alkyl, alkoxy or -$NR^{10}R^{11}$ radical and a group of two substituents together representing a methylenedioxy or ethylenedioxy radical, or also Q represents a -COPh, -SO_2Ph or –CH_2Ph radical, said -COPh, -SO_2Ph or –CH_2Ph radical being optionally substituted on its aromatic part by one or more of the substituents chosen independently from an alkyl or alkoxy radical and a halogen atom,

R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a COR^{12} group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted

heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{12} representing a hydrogen atom, an alkyl or alkoxy or $NR^{13}R^{14}$ radical,

R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle with 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{22} representing a hydrogen atom, an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,

R^{23} and R^{24} representing, independently, a hydrogen atom, an alkyl radical or a -CO-R^{25} radical,

R^{25} representing an alkyl radical,

and R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, the OH or SR^{26} group, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,

R^{26} representing a hydrogen atom or an alkyl radical,

R^{27} and R^{28} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{29}$ group, or R^{27} and R^{28} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,

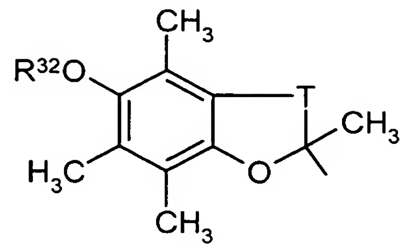
q representing an integer from 0 to 2,

R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

R^{29} representing a hydrogen atom, an alkyl, alkoxy or $-NR^{30}R^{31}$ radical,

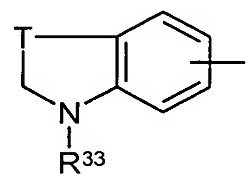
R^{30} and R^{31} representing, independently, a hydrogen atom or an alkyl radical, or R^{30} and R^{31} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,

or a



radical in which R^{32} represents a hydrogen atom or an alkyl radical, and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

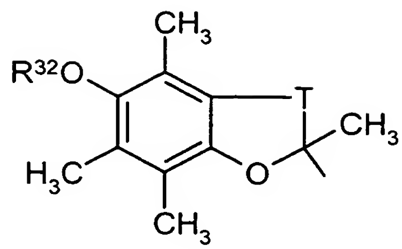
or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,
Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,
R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,
R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical,
R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

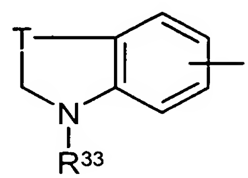
or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^{38},



radical in which R^{32} represents a hydrogen atom or an alkyl radical,
and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or finally a



radical in which R^{33} represents a hydrogen atom or an alkyl, $-\Sigma-NR^{34}R^{35}$ or $-\Sigma-CHR^{36}R^{37}$ radical,
Σ representing a linear or branched alkylene radical containing 1 to 6 carbon atoms,
R^{34} and R^{35} representing, independently, a hydrogen atom or an alkyl radical,
R^{36} and R^{37} representing, independently, a hydrogen atom or a carbocyclic or heterocyclic aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro, alkoxy or $NR^{10}R^{11}$ radicals,
R^{10} and R^{11} representing, independently, a hydrogen atom, an alkyl radical or a $-COR^{12}$ group, or R^{10} and R^{11} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
R^{12} representing a hydrogen atom or an alkyl, alkoxy or $NR^{13}R^{14}$ radical,
R^{13} and R^{14} representing, independently, a hydrogen atom or an alkyl radical, or R^{13} and R^{14} forming together with the nitrogen atom an optionally substituted heterocycle containing 4 to 7 members and 1 to 3 heteroatoms including the nitrogen atom already present, the additional heteroatoms being chosen independently from the group constituted by the O, N and S atoms,
and T represents a $-(CH_2)_m-$ radical with m = 1 or 2,

or also A represents an alkyl, cycloalkyl or cycloalkylalkyl radical;

X represents S or NR^{38},

R^{38} representing a hydrogen atom or an alkyl, cyanoalkyl, aralkyl, alkylcarbonyl or aralkylcarbonyl radical,

Y represents O or S;

R^1 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, $-(CH_2)_g-Z^1R^{39}$, $-(CH_2)_g-COR^{40}$, $-(CH_2)_g-NHCOR^{70}$, aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radical, the aryl group of the aryl, aralkyl, arylcarbonyl, heteroarylalkyl or aralkylcarbonyl radicals being itself optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, alkoxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^2R^{39}$ or $-(CH_2)_k-COR^{40}$ radicals,

Z^1 and Z^2 representing a bond, -O-, $-NR^{41}-$ or -S-,

R^{39} and R^{41} representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl or cyanoalkyl radical,

R^{40} representing, independently each time that it occurs, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{42}R^{43}$ radical,

R^{42} and R^{43} representing, independently each time that they occur, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^2 represents a hydrogen atom, an alkyl, aminoalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, trifluoromethylalkyl or $-(CH_2)_g-NHCOR^{71}$ radical, or also one of the aralkyl or heteroarylalkyl radicals optionally substituted on the aryl or heteroaryl group by one or more of the groups chosen independently from the group composed of a halogen atom and an alkyl, alkoxy, hydroxy, cyano, nitro, amino, alkylamino or dialkylamino radical,

R^{70} and R^{71} representing independently an alkyl or alkoxy radical;

or R^1 and R^2, taken together with the carbon atom which carries them, form a carbocycle with 3 to 7 members;

B represents a hydrogen atom, an alkyl radical, a $-(CH_2)_g-Z^3R^{44}$ radical or a carbocyclic aryl radical optionally substituted 1 to 3 times by the radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

Z^3 representing a bond, -O-, $-NR^{45}-$ or -S-,

R^{44} and R^{45} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical;

Ω represents one of the $NR^{46}R^{47}$ or OR^{48} radicals, in which:

R^{46} and R^{47} represent, independently, a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, $-(CH_2)_g-Z^4R^{50}$, $-(CH_2)_k-COR^{51}$, $-(CH_2)_k-COOR^{51}$, $-(CH_2)_k-CONHR^{51}$ or $-SO_2R^{51}$ radical, or also a radical chosen from the aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl and in particular pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals, the aryl or heteroaryl group of said aryl, aralkyl, aryloxyalkyl, arylcarbonyl, arylimino, aralkylcarbonyl, heteroaryl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more of the substituents chosen independently from halogen, alkyl, alkoxy, hydroxy, nitro, cyano, cyanoalkyl, amino, alkylamino, dialkylamino, $-(CH_2)_k-Z^5R^{50}$, $-(CH_2)_k-COR^{51}$ and $-(CH_2)_k-COOR^{51}$,

Z^4 and Z^5 representing a bond, -O-, $-NR^{52}-$ or -S-,

or R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S- and -CO-,

R^{50} and R^{52}, representing, independently each time that they occur, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{51} representing, independently each time that they occur, a hydrogen atom, one of the cycloalkyl or cycloalkylalkyl radicals in which the cycloalkyl radical contains 3 to 7 carbon atoms, a linear or branched alkyl radical containing 1 to 8 carbon atoms, an alkenyl, alkynyl, allenyl, allenylalkyl, cyanoalkyl, alkoxyalkyl or $NR^{58}R^{59}$ radical, or also an aryl or aralkyl radical, said aryl or aralkyl radical being able to be substituted by one or more the substituents chosen independently from a halogen atom and an alkyl or alkoxy radical,

R^{58} and R^{59} representing, independently, a hydrogen atom or an alkyl, alkenyl, alkynyl, allenyl, allenylalkyl or cyanoalkyl radical,

R^{53} and R^{54} representing, independently, a hydrogen atom or a $-(CH_2)_k-Z^7R^{60}$ or $-(CH_2)_k-COR^{61}$ radical,

Z^7 representing a bond, -O-, $-NR^{62}-$ or -S-,

R^{60} and R^{62} representing, independently, a hydrogen atom or an alkyl, alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl, aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radical, the aryl or pyridinyl group of the aryl, aralkyl, arylcarbonyl, aralkylcarbonyl, pyridinyl, pyridinylalkyl or pyridinylcarbonyl radicals being optionally substituted by one or more substituents chosen from the group constituted by the alkyl, halogen, nitro, alkoxy, cyano, cyanoalkyl, $-(CH_2)_k-Z^8R^{63}$ and $-(CH_2)_k-COR^{64}$ radicals,

R^{61} representing a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{65}R^{66}$ radical,
R^{65} and R^{66} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,
Z^8 representing a bond, -O-, $-NR^{67}-$ or -S-,
R^{63} and R^{67} representing, independently, a hydrogen atom, an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,
R^{64} representing a hydrogen atom, an alkyl, allenylalkyl, alkenyl, alkenyl, alkynyl, cyanoalkyl, alkoxy or $NR^{68}R^{69}$ radical,
R^{68} and R^{69} representing, independently, a hydrogen atom or an alkyl, allenyl, allenylalkyl, alkenyl, alkynyl or cyanoalkyl radical,

and R^{48} represents a hydrogen atom or an alkyl, alkynyl or cyanoalkyl radical;

g and p, each time that they occur, being independently integers from 1 to 6, and k and n, each time that they occur, being independently integers from 0 to 6;

it being understood that when Het is such that the compound of general formula **(III)** corresponds to general sub-formula $\mathbf{(III)}_4$, then:

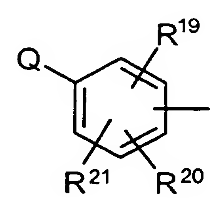
A represents the 4-hydroxy-2,3-di-tertiobutyl-phenyl radical;

B, R^1 and R^2 all represent H; and finally

Ω represents OH;

it being also understood that at least one of the following characteristics must be present:

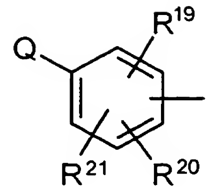
- when A represents a



radical in which Q represents OH,

Ω does not represent an $NR^{46}R^{47}$ radical in which R^{46} or R^{47} are chosen from a hydrogen atom and an alkyl radical or an $NR^{46}R^{47}$ radical in which R^{46} or R^{47} represents an aminophenyl, nitrophenyl, aminophenylcarbonyl, nitrophenylcarbonyl, aminophenylalkyl or nitrophenylalkyl radical;

- A represents a



radical B represents a carbocyclic aryl radical optionally substituted 1 to 3 times by radicals chosen from the group composed of a halogen atom, a linear or branched alkyl or alkoxy radical containing 1 to 6 carbon atoms, a hydroxy, cyano or nitro radical, an amino, alkylamino or dialkylamino radical and a carbocyclic aryl radical,

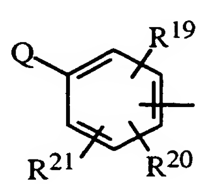
and one of R^1 and R^2 represents one of the optionally substituted arylalkyl or heteroarylalkyl radicals;

- A represents a cycloalkyl or cycloalkylalkyl radical;
- Ω represents $NR^{46}R^{47}$ and one of R^{46} and R^{47} represents an alkenyl, allenyl, allenylalkyl, alkynyl, cyanoalkyl or hydroxyalkyl radical;
- one of R^1 and R^2 represents a cycloalkyl or cycloalkylalkyl radical;
- none of R^1 and R^2 represent H;
- n = 1 and A represents a biphenyl, phenoxyphenyl, phenylthiophenyl, phenylcarbonylphenyl or phenylsulphonylphenyl radical;
- when Het is a thiazole ring and Ω represents the OR^{48} radical in which R^{48} is a cyanoalkyl radical, then the cyano group is not attached to the carbon atom immediately adjacent to the oxygen atom;

or the salts of the compounds of general formula **(III)**.

According to one of the preferred variants of the invention, the compounds of general formula **(III)** will be both ROS and MAO inhibitors and have at least one of the following characteristics:

- A representing the:



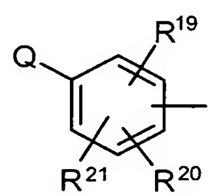
radical in which Q represents OH, two of the R^{19}, R^{20} and R^{21} radicals represent radicals chosen independently from the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals and the third represents a radical chosen from a hydrogen atom and the alkyl, alkoxy, alkylthio, amino, alkylamino or dialkylamino radicals;

- n representing 0 or 1;
- R^1 and R^2 both representing H;
- Ω representing OH or the $NR^{46}R^{47}$ radical in which one of R^{46} and R^{47} represents a cyanoalkyl radical and the other represents H or alkyl or also in which R^{46} and R^{47} taken together form with the nitrogen atom a non aromatic heterocycle with 4 to 8 members, the elements of the chain being chosen from a group composed of $-CH(R^{53})-$, $-NR^{54}-$, -O-, -S-, -CO-, R^{53} and R^{54} being as defined in general formula **(III)**.

According to another preferred variant of the invention, the compounds of general formula **(III)** will be modulators of the sodium channels and preferably have one of the following two characteristics:

– n = 0,

A represents a



radical in which Q represents a hydrogen atom or an $-OR^{22}$ or $-SR^{22}$ radical in which R^{22} represents an alkyl radical or an aryl radical optionally substituted by one or more substituents chosen from the alkyl, OH, halogen, nitro and alkoxy radicals,
R^{19}, R^{20} and R^{21} represent, independently, a hydrogen, a halogen, an SR^{26} radical, or an alkyl, cycloalkyl, alkenyl, alkoxy, cyano, nitro, $-SO_2NHR^{49}$, $-CONHR^{55}$, $-S(O)_qR^{56}$, $-NH(CO)R^{57}$, $-CF_3$, $-OCF_3$ or $NR^{27}R^{28}$ radical,
R^{26} representing an alkyl radical,
R^{27} and R^{28} representing, independently, a hydrogen atom or an alkyl radical or R^{27} and R^{28} forming together with the nitrogen atom which carries them a heterocycle with 5 to 6 members chosen from $-CH_2-$, -NH- and -O-,

R^{49} and R^{55} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkylcarbonyl radical,

q representing an integer from 0 to 2,

R^{56} and R^{57} representing, independently each time that they occur, a hydrogen atom or an alkyl or alkoxy radical,

and one of R^1 and R^2 represents a cycloalkyl or cycloalkylalkyl radical or none of R^1 and R^2 represents a hydrogen atom; or finally

– n = 1,

A represents a biphenyl or cyclohexylphenyl radical,

B represents a hydrogen atom,

R^1 and R^2 each represent a hydrogen atom,

and Ω represents an $NR^{46}R^{47}$ radical in which R^{46} represents a–$COOR^{51}$ radical, R^{51} representing an alkyl, cycloalkyl, cycloalkylalkyl or alkoxyalkyl radical and R^{47} representing a hydrogen atom.

More preferentially, the compounds of general formula **(III)** which are modulators of the sodium channels are such that Het represents an imidazole ring (i.e. that they correspond to one of general formulae **(III)**$_1$ or **(III)**$_2$ in which X represents an NR^{38} radical in which R^{38} is as defined previously).

Generally, the compounds of general formula **(III)** will be preferably chosen from the compounds described (sometimes in the form of salts) in Examples 1 to 7, 9, 10, 24, 26 to 35, 52, 57, 61, 80, 82, 83, 85 to 87, 90, 94, 113, 115, 123, 127, 130, 132, 134, 138, 139, 147, 152, 154, 161, 164, 169, 171 to 173, 176 to 180, 203, 237 to 239, 243 to 247, 249, 251, 255, 258 to 262, 264 to 271, 273 to 275, 277 to 333 and 335 to 349, or the salts of these compounds.

More preferentially, the compounds of general formula **(III)** will be chosen from the compounds described (sometimes in the form of salts) in Examples 1, 3, 6, 7, 24, 26 to 35, 57, 61, 82, 83, 85 to 87, 94, 113, 123, 130, 132, 134, 138, 139, 152, 154, 164, 169, 171 to 173, 176 to 178, 203, 237 to 239, 243 to 247, 249, 255, 258, 259, 261, 262, 264 to 271, 273 to 275, 277 to 281, 283 to 288, 293 to 313, 321, 323, 324, 332 and 338 to 340, or the salts of these compounds.

The same preferences as those indicated for the compounds of general formula **(I)** and **(II)** are moreover applicable by analogy to the compounds of general formula **(III)**.

In certain cases, the compounds according to the present invention (i.e. the compounds of general formula **(I)**, **(II)** or **(III)**) can contain asymmetrical carbon atoms. As a result, the compounds according to the present invention have two possible enantiomeric forms, i.e. the "R" and "S" configurations. The present invention includes the two enantiomeric forms and all combinations of these forms, including the racemic "RS" mixtures. For the sake of simplicity, when no specific configuration is indicated in the structural formulae, it should be understood that the two enantiomeric forms and their mixtures are represented.

The invention also relates to of the pharmaceutical compositions containing, as active ingredient, a compound of general formula **(II)** or a pharmaceutically acceptable salt of a compound general formula **(II)**, as well as the use of the compounds of general formula **(II)** for preparing a medicament intended to inhibit the monoamine oxydases, in particular monoamine oxydase B, to inhibit lipidic peroxidation, to have a modulatory activity on the sodium channels or to have two of the three or all three aforementioned activities.

The invention relates moreover, as medicaments, to the compounds of general formula **(III)** or their pharmaceutically acceptable salts. Similarly it relates to the pharmaceutical compositions containing, as active ingredient, a compound of general formula **(III)** or a pharmaceutically acceptable salt of a compound of general formula **(III)**, as well as to the use of the compounds of general formula **(III)** for preparing a medicament intended to inhibit monoamine oxydases, in particular monoamine oxydase B, to inhibit lipidic peroxidation, to have a modulatory activity on the sodium channels or to have two of the three or all three of the aforementioned activities.

In particular, the compounds of general formula **(I)**, **(II)** or **(III)** can be used for preparing a medicament intended to treat one of the following disorders or one of the following diseases: Parkinson's disease, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, schizophrenia, depressions, psychoses, migraine or pains and in particular neuropathic pains.

By pharmaceutically acceptable salt, is meant in particular the addition salts with inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, diphosphate and nitrate or with organic acids such as acetate, maleate, fumarate, tartrate, succinate, citrate, lactate, methanesulphonate, p-toluenesulphonate, pamoate and stearate. Also included in the field of the present invention, when they can be used, are the salts formed from bases such as sodium or potassium hydroxide. For other

examples of pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

The pharmaceutical composition can be in the form of a solid, for example powders, granules, tablets, gelatin capsules, liposomes or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax.

The pharmaceutical compositions containing a compound of the invention can also be presented in liquid form, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols, similarly their mixtures, in varying proportions, in water.

The administration of a medicament according to the invention can be done by topical, oral, parenteral route, by intramuscular injection, etc.

The administration dose envisaged for a medicament according to the invention is comprised between 0.1 mg to 10 g according to the type of active compound used.

In accordance with the invention, the compounds of general formula **(I)** can be prepared by the processes described below.

PREPARATION OF THE COMPOUNDS OF THE INVENTION:

Generalities

The preparations of the compounds of the invention which correspond to general formulae **(I)**, **(II)** or **(III)** in which Ω represents OH are carried out in a similar fashion to those described in the PCT Patent Application WO 99/09829 and the European Patent Application EP 432 740.

As regards the compounds of the invention which correspond to general formulae **(I)**, **(II)** and **(III)** and in which Het is an imidazole ring, a person skilled in the art can also usefully consult the PCT Patent Application WO 99/64401.

The preparations of the other compounds of the invention which correspond to general formulae **(I)**, **(II)** and **(III)** are carried out in a similar fashion to those described in the PCT Patent Application WO 98/58934 (*cf. in particular on pages 39 to 45 of this*

document the syntheses of intermediates of general formulae (XXV) and (XXVIII)) or according to the procedures described hereafter.

Preparation of the compounds of general formula (I)

The compounds of general formula **(I)** can be prepared by the 8 synthesis routes illustrated below (Diagram 1) starting from the intermediates of general formula **(IV)**, **(V)**, **(VI)**, **(VII)**, **(VIII)**, **(IX)**, **(X)** and **(I)*a*** in which A, B, Ω, R^1, R^2, Het and n are as defined above, L is a parting group such as for example a halogen, Alk is an alkyl radical, Gp is a protective group for an amine function, for example a 2-(trimethylsilyl)ethoxymethyl (SEM) group, and Gp' a protective group for an alcohol function, for example a group of benzyl, acetate or also silyl type such as *tert*-butyldimethylsilyl, and finally Λ represents a bond or a $-(CH_2)_x-$, $-CO-(CH_2)_x-$, $-(CH_2)_y-O-$ or $-C(=NH)-$ radical. Of course, a person skilled in the art can choose to use protective groups other than Gp and Gp' from those which are known, and in particular those mentioned in: *Protective groups in organic synthesis*, 2nd ed., (John Wiley & Sons Inc., 1991).

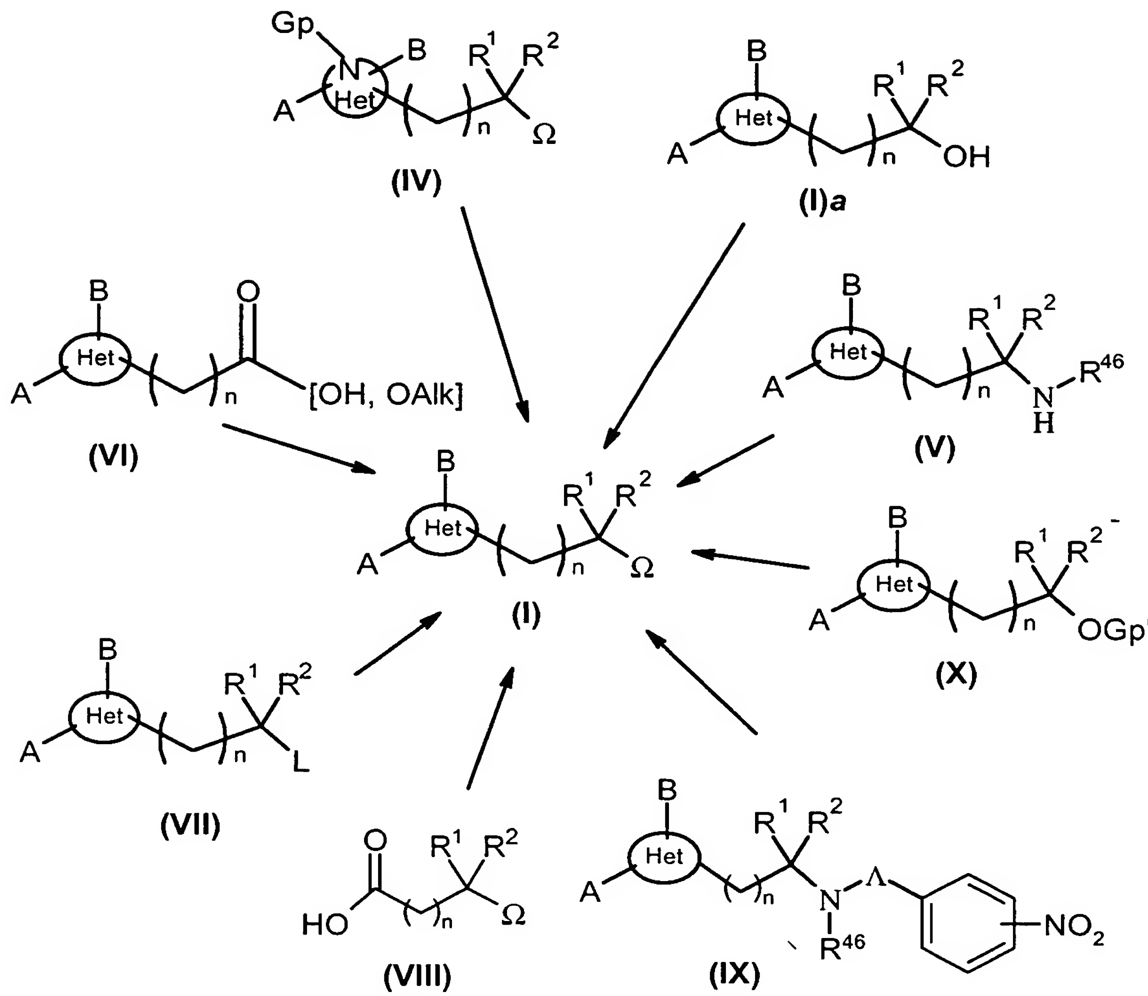


Diagram 1

<u>Route 1:</u> Het is imidazole and Ω is $NR^{46}R^{47}$ but not a radical of carbamate type

The amines and carboxamides of general formula **(I)**, Diagram 2, in which A, B, R^1, R^2, R^{46}, R^{47}, Het and n are as defined above, are prepared by deprotection for example, in the case where Gp represents SEM, with *tert*-butylammonium fluoride (TBAF) in THF, of the amine of general formula **(IV)** in order to release the amine of the heterocycle of the compound of general formula **(I)**. The protected amines of general formula **(IV)** are accessible by a general synthesis route described in *Biorg. and Med. Chem. Lett.*, 1993, **3,** 915 and *Tetrahedron Lett.*, 1993. **34**, 1901 and more particularly in the PCT Patent Application WO 98/58934.

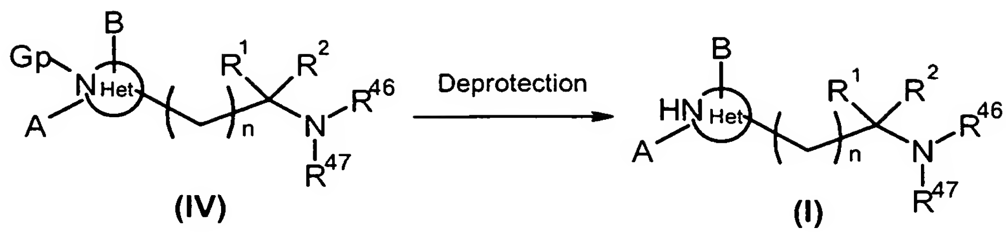


Diagram 2

<u>**Route 2:**</u> Het is imidazole, oxazole or thiazole and Ω is $NR^{46}R^{47}$

The amines and carboxamides of general formula **(I)**, Diagram 3, in which A, B, R^1, R^2, R^{46}, Het, g, k and n are as defined above, Δ represents an alkyl, cycloalkylalkyl, arylalkyl, aryl, allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl or hydroxyalkyl radical and Δ' represents an alkyl, cycloalkylalkyl, arylalkyl or aryl radical when g or k do not represent 0, or Δ' represents an alkyl, cycloalkylalkyl, arylalkyl radical or an aryl radical preferably deactivated (i.e. an aryl radical substituted by an electron attractor group such as for example a nitro or cyano group) when g or k represents 0, are prepared by condensation of the amines of general formula **(V)** with carboxylic acids (or the corresponding acid chlorides) of general formula **(XIII)** under standard conditions of peptide synthesis, with the aldehydes of general formula **(XII)** in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium borohydride, in a lower aliphatic alcohol such as methanol and optionally in the presence of molecular sieves, or with halogenated derivatives (Hal = halogen atom) of general formula **(XI)**. In particular, when Δ represents an allenyl, allenylalkyl, alkenyl, alkynyl, cyanoalkyl or hydroxyalkyl radical, the compounds of general formula **(V)** are converted to the corresponding compounds of general formula **(I)** by reaction with the halogenated derivatives of general formula **(XI)** in a solvent such as acetonitrile, dichloromethane or acetone and in the presence of a base such as for example triethylamine or potassium carbonate at a temperature comprised between ambient temperature and the reflux temperature of the solvent.

The derivatives of general formula **(V)** are in particular accessible by a general synthesis route described in *Biorg. and Med. Chem. Lett.*, 1993, **3,** 915 and *Tetrahedron Lett.*, 1993. **34**, 1901, and more particularly in the Patent Application WO 98/58934. When R^{46} = H, the compounds of general formula **(V)** can be prepared, for example, according to a protocol described in the Patent Application WO 98/58934 (using the appropriate amino acid in place of N-Boc-sarcosinamide).

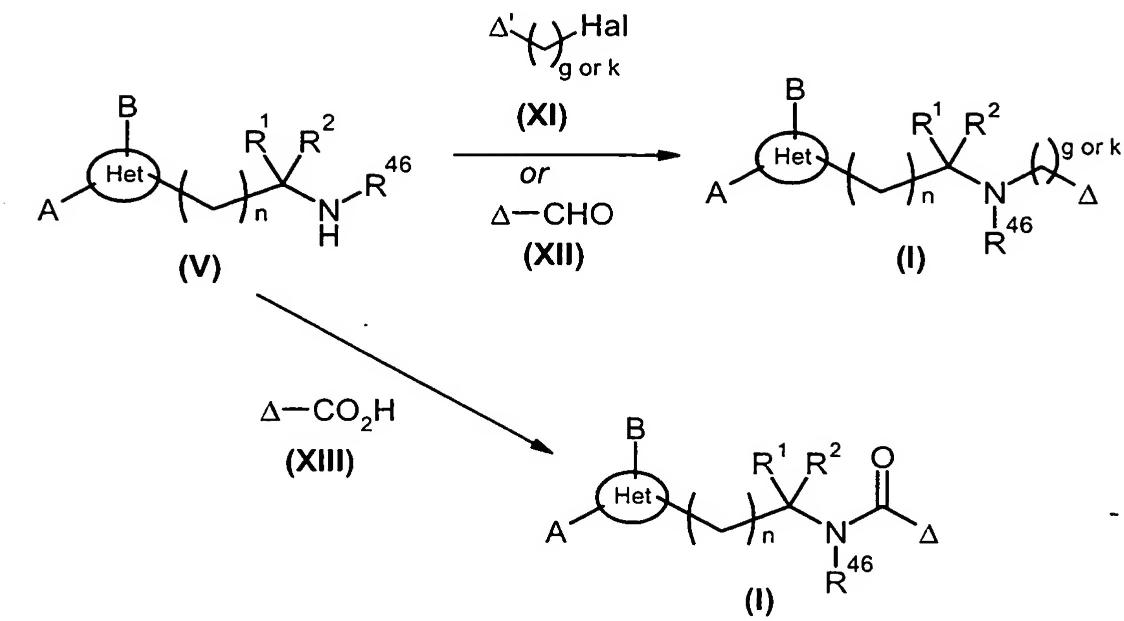


Diagram 3

In the particular case where R^{47} represents a cycloalkyl radical, the amines of general formula **(I)**, Diagram 3a, in which A, B, R^1, R^2, R^{46}, Het and n are as defined above and i represents an integer from 0 to 4 are prepared by condensation of the amines of general formula **(V)** with the cycloalkylketones of general formula **(XIV)** in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium borohydride in a lower aliphatic alcohol such as methanol and optionally in the presence of molecular sieves at ambient temperature.

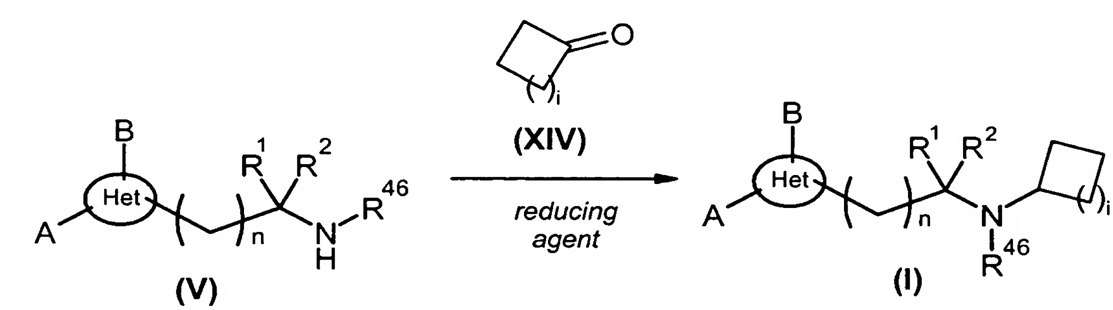


Diagram 3a

The sulphonamides of general formula **(I)**, Diagram 3b, in which A, B, R^1, R^2, R^{46}, Het and n are as defined above, R^{47} represents an -SO_2-Δ radical and Δ represents an alkyl, cycloalkyl, cycloalkylalkyl or arylalkyl radical, are prepared by condensation of the amines of general formula **(V)** with the sulphochlorides of general formula **(XV)** under

standard conditions, for example in a solvent such as dimethylformamide at ambient temperature.

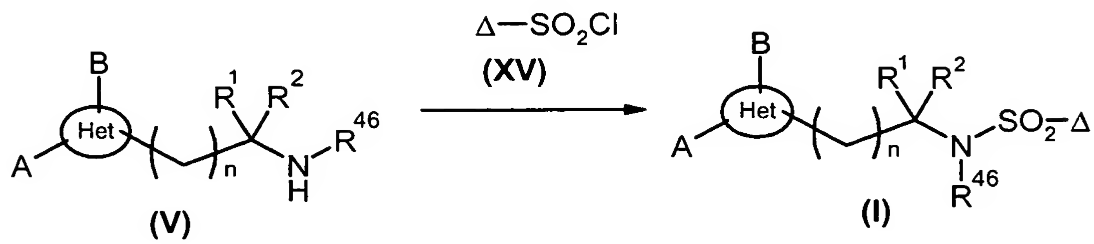


Diagram 3b

The ureas of general formula **(I)**, Diagram 3c, in which A, B, R^1, R^2, R^{46}, Het and n are as defined above, R^{47} represents a -CO-NH-Δ radical and Δ represents an alkyl, cycloalkyl, cycloalkylalkyl or arylalkyl radical, are prepared by reaction of the amines of general formula **(V)** with the isocyanates of general formula **(XVI)** in an inert solvent such as dichloromethane or 1,2-dichloroethane.

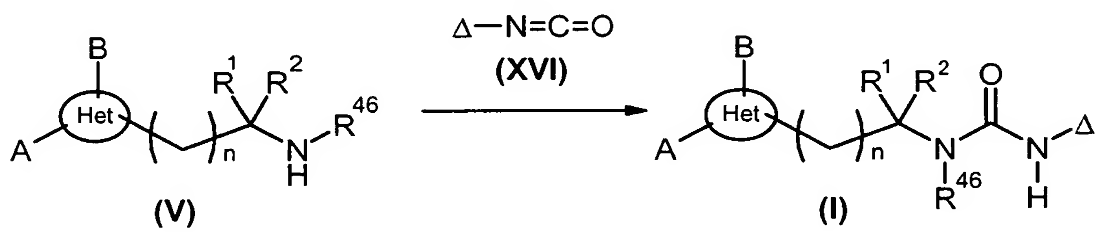
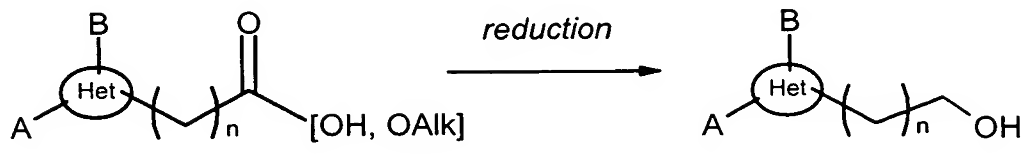


Diagram 3c

__Route 3:__ Het is oxazole or thiazole, R^1 and R^2 are both H and Ω is OH.

The alcoholic derivatives of general formula **(I)**, Diagram 4, in which A, B, Het and n are as defined above and R^1 and R^2 are hydrogen atoms are obtained by reduction of the acids or esters of general formula **(VI)** (accessible by a general synthesis route described in *J.Med Chem.*, 1996, **39,** 237-245 and the PCT Patent Application WO 99/09829). This reduction can, for example, be carried out by the action of boron hydride or lithium aluminium hydride or also diisobutylaluminium hydride in an aprotic polar solvent such as tetrahydrofuran.

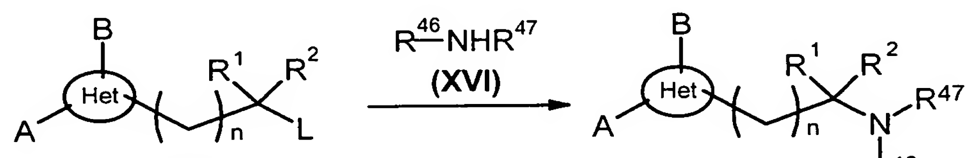


(VI) (I)

Diagram 4

<u>Route 4</u>: Het is oxazole or thiazole and Ω is $NR^{46}R^{47}$.

The amines of general formula **(I)**, Diagram 5, in which A, B, R^1, R^2, R^{46}, R^{47}, Het, and n are as defined above, are prepared by condensation of the primary or secondary amines of general formula R^{46}-NHR^{47} with the compounds of general formula **(VII)** (in which L preferably represents a halogen atom Hal, but can also represent a mesylate or tosylate group) according to a general synthesis route described in *J. Med. Chem.*, 1996, **39**, 237-245 and the PCT Patent Application WO 99/09829 or the US Patent 4,123,529. This synthesis route can in particular be used when R^{46} and R^{47} taken together form with the nitrogen atom which carries them a non-aromatic heterocycle with 4 to 8 members. The reaction typically takes place in an anhydrous solvent (for example dimethylformamide, dichloromethane, tetrahydrofuran or acetone) in the presence of a base (for example Na_2CO_3 or K_2CO_3 in the presence of triethylamine), and preferably while heating.



(VII) (I)

Diagram 5

<u>Route 5:</u> Het is imidazole and Ω is a radical of carbamate type

When Ω is a radical of carbamate type, the acids of general formula **(VIII)** can be cyclized in the form of derivatives of imidazoles of general formula **(I)**, Diagram 6, by the addition of caesium carbonate followed by a condensation with an α-halogenoketone of formula A-CO-CH(B)-[Br, Cl] followed by the addition of a large excess of ammonium acetate (for example 15 or 20 equivalents per equivalent of acid of general formula **(VIII)**). This reaction is preferably carried out in a mixture of xylenes

and while heating (one can also, if appropriate, simultaneously eliminate the water formed during the reaction).

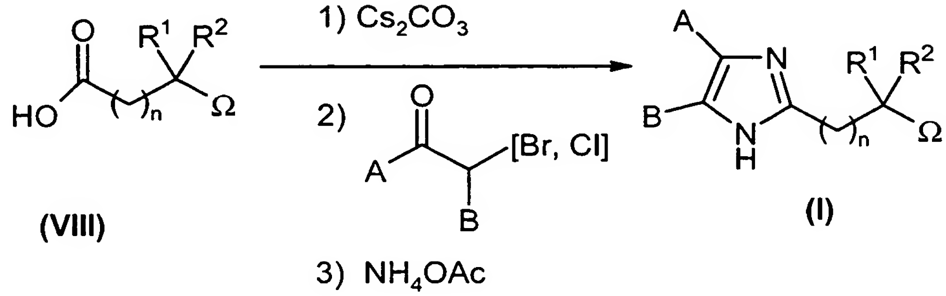


Diagram 6

Route 6: Het is imidazole, oxazole or thiazole and Ω is $NR^{46}R^{47}$

When Ω is an $NR^{46}R^{47}$ radical in which R^{47} is a radical comprising a termination of aminophenylene, alkylaminophenylene or dialkylaminophenylene type, the compounds of general formula **(I)**, in which A, B, Het, n, R^1, R^2 and R^{46} are as defined above and Λ represents a bond or a $-(CH_2)_x-$, $-CO-(CH_2)_x-$, $-(CH_2)_y-O-$ or $-C(=NH)-$ radical, x and y being integers from 0 to 6, can be obtained, Diagram 7, by reduction of the compound of general formula **(IX)**, for example by the action of hydrogen in the presence of a catalyst of palladium on carbon type in a solvent such as for example methanol, ethanol, dichloromethane or tetrahydrofuran. Reduction of the nitro function can also be carried out, for example, by heating the product in an appropriate solvent such as ethyl acetate with a little ethanol in the presence of $SnCl_2$ (*J. Heterocyclic Chem.* (1987), **24**, 927-930; *Tetrahedron Letters* (1984), **25** (8), 839-842) or in the presence of $SnCl_2$ / Zn (*Synthesis.* (1996),9,1076-1078), using $NaBH_4$-$BiCl_3$ (*Synth. Com.* (1995) 25 (23), 3799-3803) in a solvent such as ethanol, or then by using Raney Ni with hydrazine hydrate added to it (*Monatshefte für Chemie*, (1995), 126, 725-732), or also using indium in a mixture of ethanol and ammonium chloride under reflux (*Synlett (1998) 9,* 1028).

When R^{47} is a radical of aminophenylene, alkylaminophenylene or dialkylaminophenylene type (Alk and Alk' are identical or different alkyl radicals), the compound of general formula **(IX)** is reduced in order to produce the aniline derivative of general formula **(I)** and optionally mono- or di-alkylated according to standard reactions known to a person skilled in the art. The mono-alkylation is carried out by reducing amination with an aldehyde or by a nucleophilic substitution by reaction with

an equivalent of halogenoalkyl Alk-Hal. A second alkylation can then be carried out if appropriate using a halogenoalkyl Alk'-Hal.

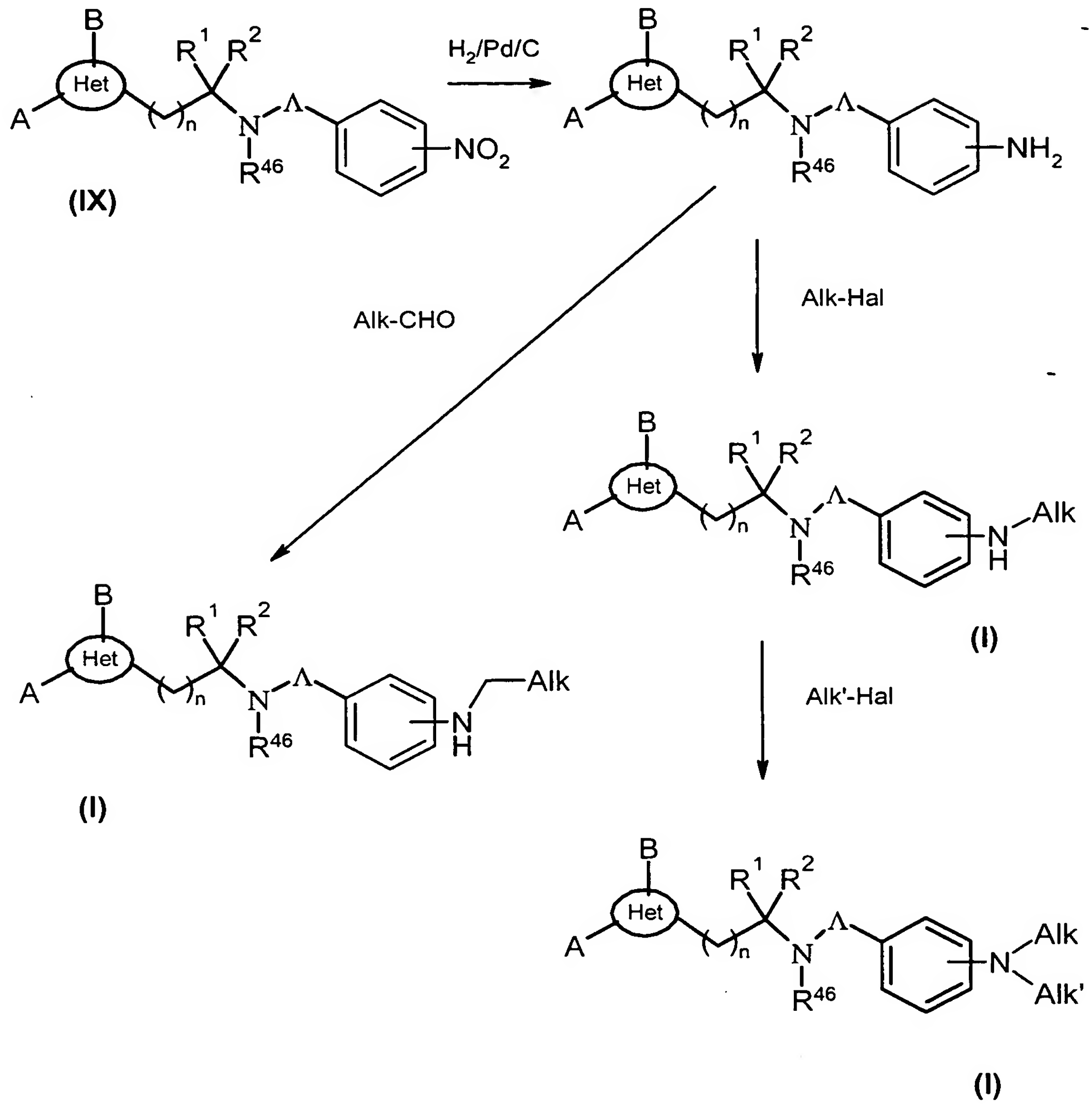


Diagram 7

In the particular case where Alk = Alk' = -CH_3 and where Λ does not represents -CH_2-, the nitro derivative of general formula **(IX)** will be treated with suitable quantities of paraformaldehyde under a flow of hydrogen in a solvent such as ethanol and in the presence of a catalyst of palladium on carbon type (Diagram 7*a*).

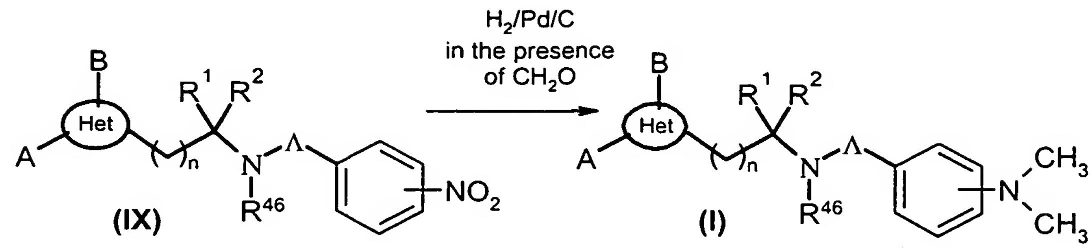


Diagram 7*a*

<u>Route 7:</u> Het is imidazole, oxazole or thiazole and Ω is OH

This route can be used when Ω is OH. Contrary to route 3, R^1 and R^2 cannot be hydrogen atoms. In this case, the compounds of general formula **(I)** can be obtained, Diagram 8, by deprotection of the protected alcohol of general formula **(X)**.

In the case where Gp' is a protective group of silyl type, the deprotection can be carried out, for example, by adding tetra-*tert*-butylammonium fluoride in a solvent such as tetrahydrofuran. In the case where Gp' is a protective group of benzyl type, the deprotection will be carried out by hydrogenation in a solvent such as for example methanol, ethanol, dichloromethane or tetrahydrofuran. In the case where Gp' is a protective group of acetate type, the deprotection can be carried out, for example, using sodium or potassium carbonate in an alcoholic solvent such as methanol. For other cases, a person skilled in the art will usefully consult the following document: *Protective groups in organic synthesis*, 2nd ed., (John Wiley & Sons Inc., 1991).

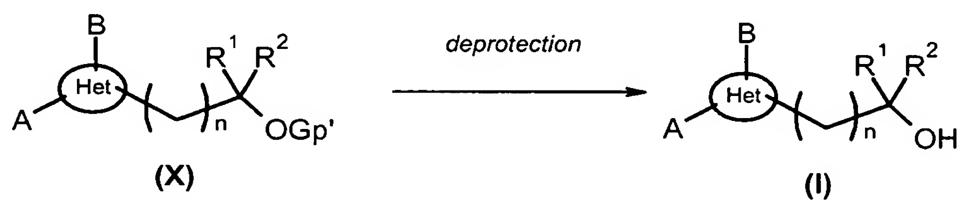


Diagram 8

<u>Route 8:</u> Het is imidazole, oxazole or thiazole and Ω is OR^{48} with R^{48} H

The compounds of general formula **(I)** in which Ω is an OR^{48} radical with R^{48} H are obtained, for example, Diagram 9, from alcohols of general formula **(I)a** (which are compounds of general formula **(I)** as defined previously in which Ω represents OH) by reacting the latter with a halide of general formula R^{48}-Hal (Hal = Br, Cl or I) in a solvent such as dichloromethane, acetonitrile, anhydrous tetrahydrofuran or anhydrous ether and in the presence of a base such as potassium or sodium carbonate, sodium hydride or triethylamine.

In the case where the A, B, R^1 and R^2 radicals contain alcohol, phenol, amine or aniline functions, it may be necessary to add protection/deprotection stage for these functions according to standard methods known to a person skilled in the art (stages not represented in Diagram 9).

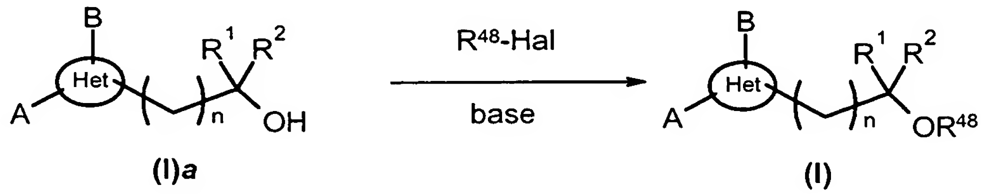


Diagram 9

Preparation of the synthesis intermediates

Preparation of the imidazoles and thiazoles of general formula (V)

General outline

The non-commercial ketonic derivative of general formula **(V.i)** or $\mathbf{(V.i)_2}$ in which A and B are as defined in general formula **(I)** is converted, Diagram 3.1, to the corresponding α-bromo-ketone of general formula **(V.ii)** ou $\mathbf{(V.ii)_2}$ by reaction with a bromination agent such as $CuBr_2$ (*J. Org. Chem.* (1964), **29**, 3459), bromine (*J. Het. Chem.* (1988), **25**, 337), N-bromosuccinimide (*J. Amer. Chem. Soc.* (1980), **102**, 2838) in the presence of acetic acid in a solvent such as ethyl acetate or dichloromethane, HBr or Br_2 in ether, ethanol or acetic acid (*Biorg. Med. Chem. Lett.* (1996), **6**(3), 253-258; *J. Med. Chem.* (1988), **31**(10), 1910-1918) *J. Am. Chem. Soc.* (1999), **121**, 24) or also using a bromination resin (*J. Macromol. Sci. Chem.* (1977), **A11**, (3) 507-514). In the particular case where A is a p-dimethylaminophenyl radical, it is possible to use the operating method appearing in the publication *Tetrahedron Lett.*, 1998, **39** (28), 4987. The amine of general formula **(V)** is then obtained according to the procedures shown in Diagrams 3.2 (imidazoles) and 3.3 (thiazoles) hereafter.

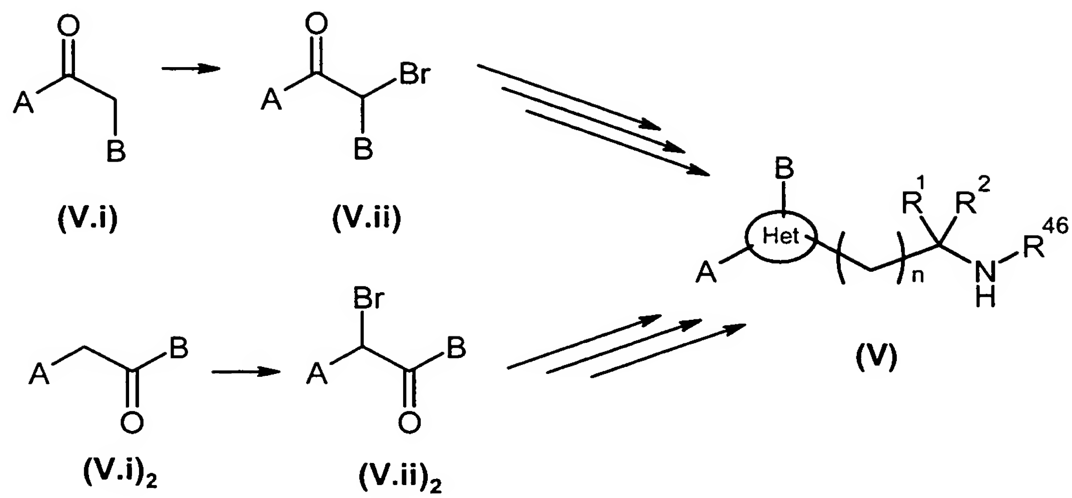


Diagram 3.1

Alternatively to the synthesis shown in Diagram 3.1, a person skilled in the art can, if appropriate, use an α-chloro-ketone in place of an α-bromo-ketone.

Obtaining the imidazoles of general formula (V)

The acid of general formula **(V.iii),** in which Gp represents a protective group for an amine function, for example a protective group of carbamate type, is treated, Diagram 3.2, with Cs_2CO_3 in a solvent such as methanol or ethanol. The α-halogeno-ketone of general formula **(V.ii)** in an inert solvent such as dimethylformamide is added to the caesium salt recovered. The intermediate ketoester is cyclized by heating to reflux in xylene (mixture of isomers) in the presence of a large excess of ammonium acetate (15 or 20 equivalents for example) in order to produce the imidazole derivative of general formula **(V.iv)** (the water formed being optionally eliminated during the reaction).

In the case where R^{38} is not H, the amine function of the imidazole ring of the compound of general formula **(V.iv)** is substituted by reaction with the halogenated derivative R^{38}-Hal (Hal = halogen atom); the protected amine function is then deprotected under standard conditions (for example: trifluoroacetic acid or HCl in an organic solvent when it is a protective group of carbamate type, or also hydrogenation in the presence of palladium on carbon when the protective group is a benzyl carbamate).

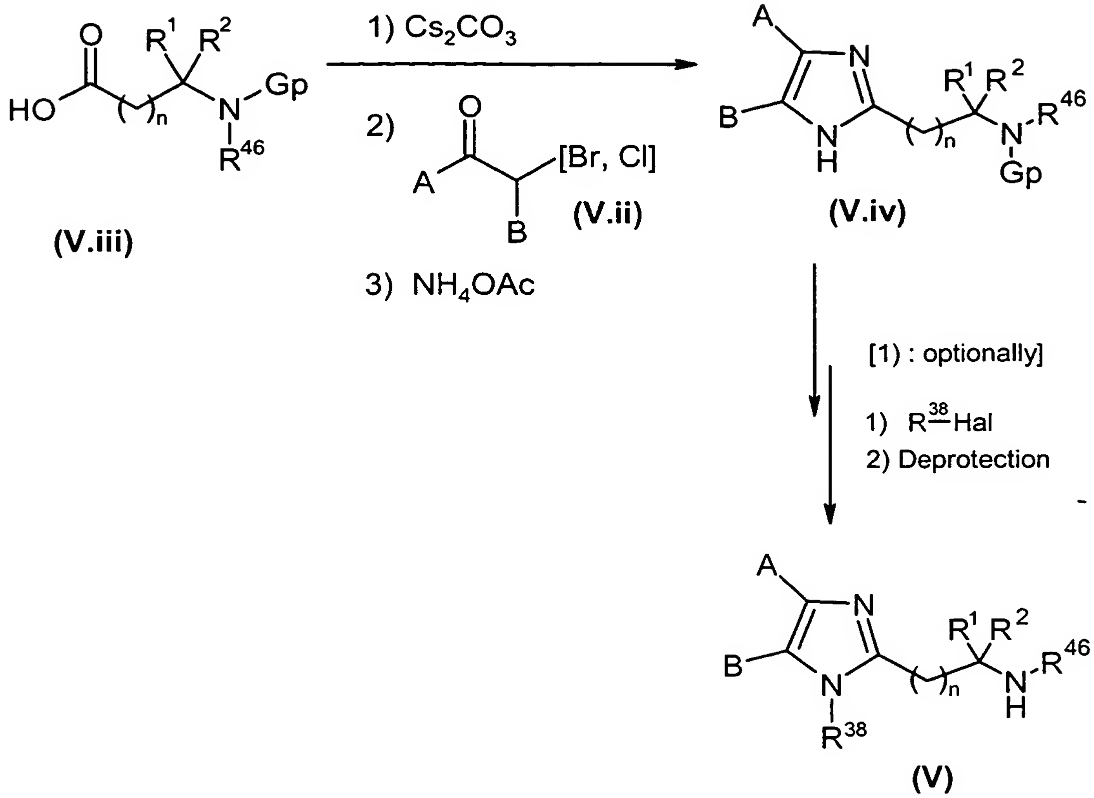


Diagram 3.2

Obtaining the thiazoles of general formula (V) intended for the preparation of compounds of general formulae $(I)_1$ or $(I)_2$:

The thiocarboxamide of general formula **(V.v)**, in which Gp represents a protective group for an amine function, for example a protective group of carbamate type, obtained for example by reaction of the corresponding carboxamide with Lawesson reagent or with $(P_2S_5)_2$, is reacted, Diagram 3.3, with the α-bromo-ketone of general formula **(V.ii)** or $\mathbf{(V.ii)_2}$ according to an experimental protocol described in the literature (*J. Org. Chem.*, (1995), **60**, 5638-5642). The protected amine function is then deprotected under standard conditions in a strong acid medium (for example: trifluoroacetic acid or HCl in an organic solvent when it is a protective group of carbamate type), releasing the amine of general formula **(V)**.

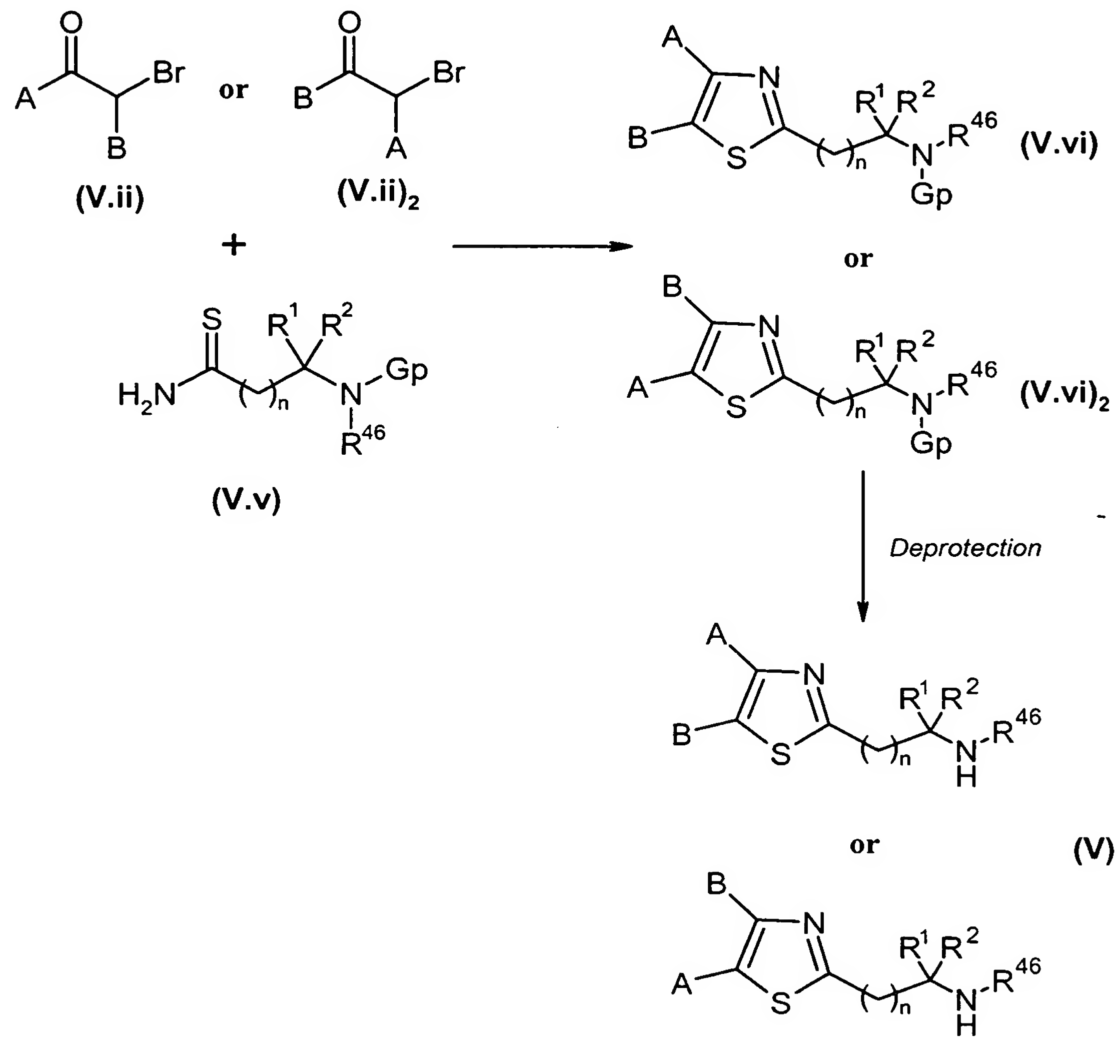


Diagram 3.3

Obtaining the thiazoles of general formula (V) intended for the preparation of compounds of general formula (I)$_3$*:*

These compounds are obtained according to a method summarized in Diagram 3.4 below. The carboxamide of general formula **(VII.ii)** is firstly treated, for example, with Lawesson reagent or with $(P_2S_5)_2$ then the thiocarboxamide of general formula **(VII.iii)** obtained is reacted with the halogenated derivative of general formula **(V.vii)** (cf. *Biorg. Med. Chem. Lett.* (1996), **6**(3), 253-258; *J. Med. Chem.* (1988), **31**(10), 1910-1918; *Tetrahedron Lett.*, (1993), **34** (28), 4481-4484; or *J. Med. Chem.* (1974), 17, 369-371; or also *Bull. Acd. Sci. USSR Div. Chem. Sci.* (Engl Transl) (1980) **29**, 1830-1833). The protected amine of general formula **(V.viii)** thus obtained is then deprotected under standard conditions for a person skilled in the art (for example: trifluoroacetic acid or HCl in an organic solvent when Gp is a protective group of carbamate type).

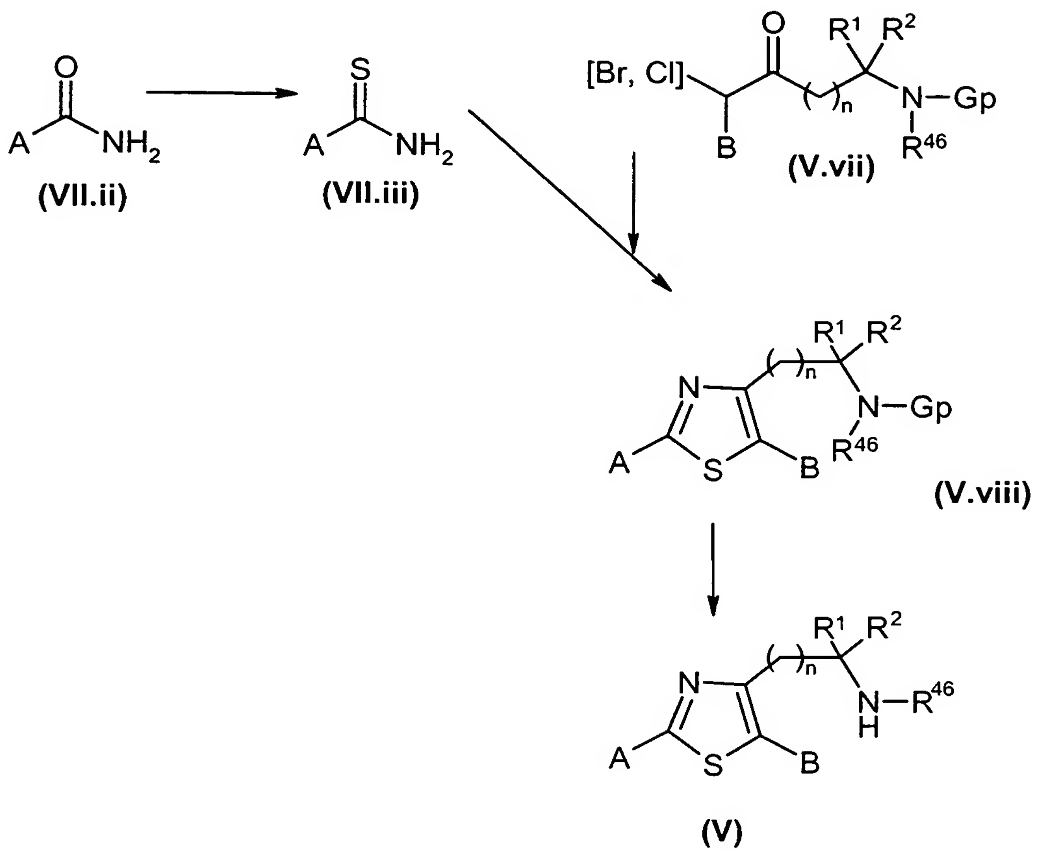


Diagram 3.4

Obtaining the oxazoles of general formula (V) intended for the preparation of compounds of general formula (I)$_3$:

These compounds are obtained according to a method summarized in Diagram 3.5 below. The carboxamide of general formula **(VII.ii)** is reacted with the halogenated derivative of general formula **(V.vii)**. The protected amine of general formula **(V.ix)** thus obtained is then deprotected under standard conditions for a person skilled in the art in order to produce the compound of general formula **(V)** (for example: trifluoroacetic acid or HCl in an organic solvent when Gp is a protective group of carbamate type).

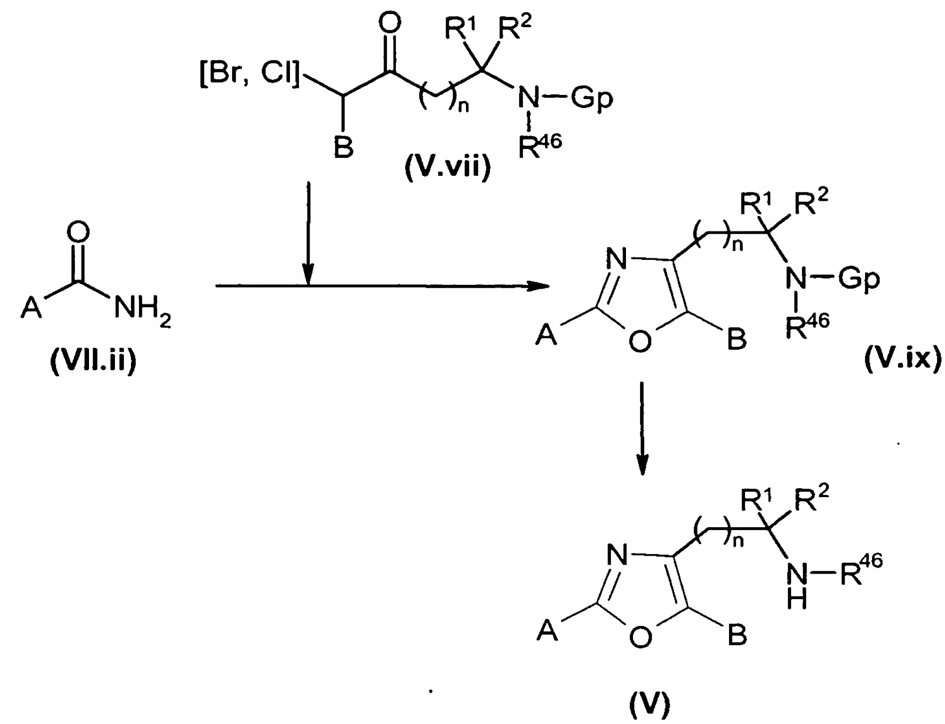


Diagram 3.5

Preparation of the ketonic derivatives of general formula (V.i) and of certain α-bromoketonic derivatives of general formula (V.ii)$_1$ (V.ii)$_2$ or (V.vii)

The non-commercial ketonic derivatives of general formula **(V.i)** or their α-bromoketonic homologues are accessible from methods in the literature or similar methods adapted by a person skilled in the art. In particular:

- when A represents an indolinyl or tetrahydroquinolyl radical, the compounds of general formula **(V.i)** are accessible from methods in the literature such as for example *J. Med. Chem.* (1986), **29**, (6), 1009-1015 or *J. Chem. Soc., Perkin Trans. 1* (1992), **24**, 3401-3406;

Alternatively, the compounds of general formula **(V.ii)** in which A represents an indolinyl or tetrahydroquinolyl radical in which R^{33} represents H can be synthesized according to a protocol which is slightly modified compared to that described in *J. Chem. Soc., Perkin Trans 1* (1992), **24**, 3401-3406. This protocol is summarized in Diagram 3.6 below.

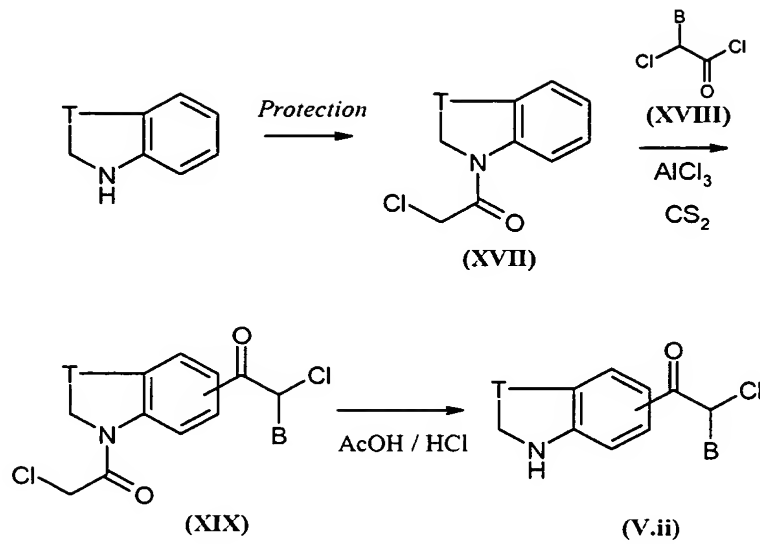


Diagram 3.6

The indoline or tetrahydroquinoline (T represents $-CH_2-$ or $-(CH_2)_2-$) is protected using chloroacetyl chloride in order to produce the compound of general formula **(XVII)** which is subjected to a Friedel-Crafts reaction (substituted chloroacetyl chloride of general formula **(XVIII)**, in which B has the meaning indicated previously, in a solvent such as carbon disulphide and in the presence of aluminium chloride) in order to produce the compound of general formula **(XIX)**. Then the compound of general formula **(XIX)** is hydrolyzed in the presence of acid, for example an acetic acid/HCl mixture, in order to produce the compounds of general formula **(V.ii)** in the form of a mixture of meta and para isomers. These isomers can be separated by fractioned crystallization from a solvent such as glacial acetic acid.

A person skilled in the art will know how to adapt the syntheses described previously to the case where A represents an indolinyl or tetrahydroquinolyl radical in which R^{33} does not represent H. For example, when R^{33} represents an alkyl or aralkyl radical, the protection and deprotection stages will be unnecessary.

- when A represents a radical of 4-(4-hydroxyphenyl)-phenyl type, the compounds of general formula **(V.i)** are accessible from methods in the literature such as for example *J. Org. Chem.*, (1994), **59**(16), 4482-4489.

Alternatively, the compounds of general formula **(V.i)** and **(V.ii)** in which A represents a radical of 4-(4-hydroxyphenyl)-phenyl type are accessible for example by the method illustrated in Diagram 3.7 below.

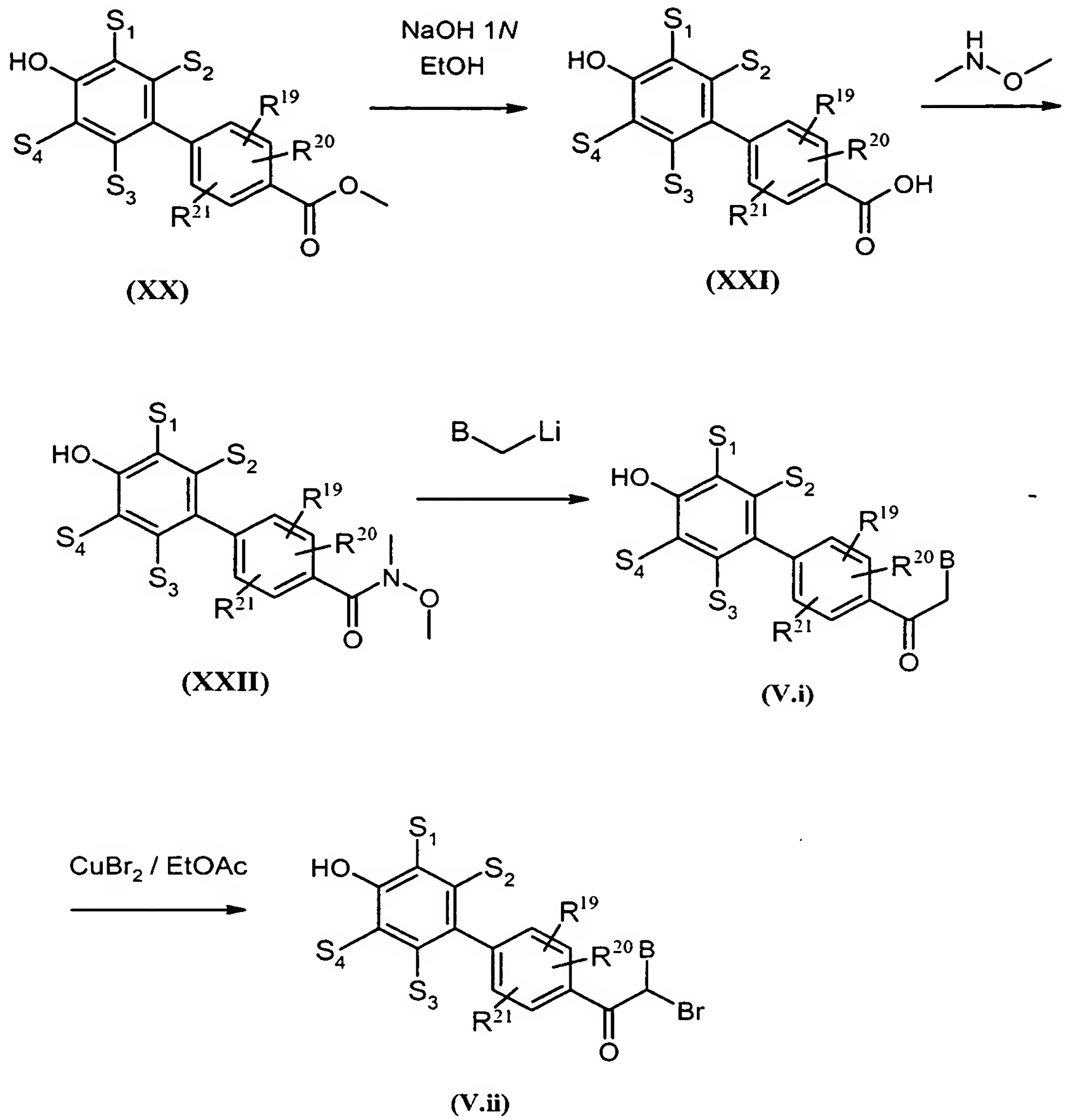


Diagram 3.7

The compounds of general formula **(V.i)** or **(V.ii)**, in which S_1, S_2, S_3 and S_4 are chosen independently from a hydrogen atom and OH, cyano, nitro, alkyl, alkoxy or $-NR^{10}R^{11}$ as defined in general formula **(I)**, are prepared, Diagram 3.7, from the esters of general formula **(XX)** (cf. in particular *Chem. Lett.* (1998), **9**, 931-932 and *Synthesis* (1993), **8**, 788-790). Of course, the phenol or aniline functions resulting from the nature of the R^{19}, R^{20}, R^{21}, S_1, S_2, S_3 and S_4 substituents can lead a person skilled in the art to add to the stages represented in Diagram 3.7 protection stages (and, subsequently in the synthesis of the compounds of general formula **(I)**, deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis. The esters of general formula **(XX)** are

hydrolyzed in order to produce the acids of general formula **(XXI)**. The latter are then subjected to coupling with N,O-dimethylhydroxylamine (*Syn. Commun.* (1995), **25**(8), 1255; *Tetrahedron Lett.* (1999), **40**(3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazole, in order to produce the intermediates of general formula **(XXII)**. The compounds of general formula **(V.i)** are prepared from the compounds of general formula **(XXII)** by a substitution reaction with MeLi (*J. Med. Chem.* (1992), **35**(13), 2392). The bromoacetophenones of general formula **(V.ii)** are now accessible from the acetophenone of general formula **(V.i)** under the conditions described previously.

- when A represents a carbazolyl radical, the compounds of general formula **(V.i)** are accessible from methods in the literature such as for example *J. Org. Chem.*, (1951), **16**, 1198 or *Tetrahedron* (1980), **36**, 3017.

Alternatively, the compounds of general formula **(V.ii)** in which A represents a carbazolyl radical in which R^9 represents H can be synthesized according to a protocol which is slightly modified with respect to that described for A = carbazolyl in *Tetrahedron* (1980), **36**, 3017. This method is summarized in Diagram 3.8 hereafter:

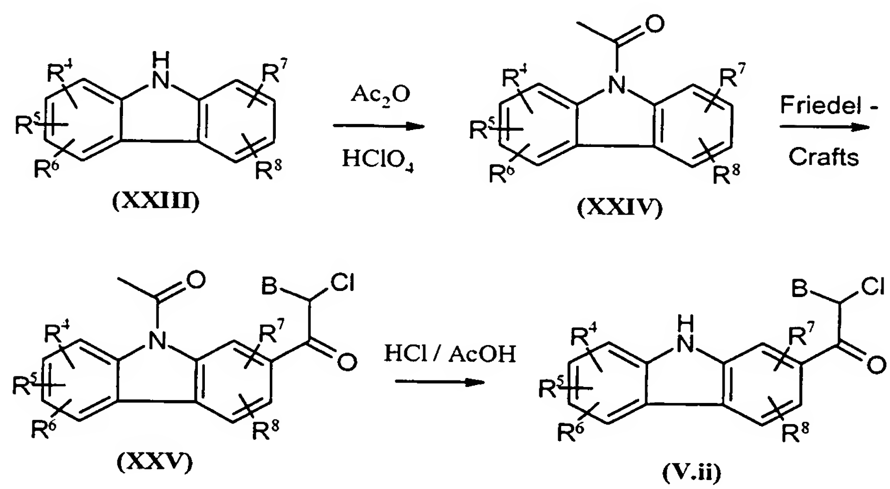


Diagram 3.8

The carbazole of general formula **(XXIII)** is protected using acetic anhydride in order to produce the compound of general formula **(XXIV)**, which is subjected to a Friedel-Crafts reaction (substituted chloroacetyl chloride of general formula **(XVIII)** as defined previously in a solvent such as carbon disulphide and in the presence of aluminium chloride) in order to produce the compound of general formula **(XXV)**.

Then the acyl group protecting the amine function is hydrolyzed in the presence of acid, for example an AcOH/HCl mixture, in order to produce the compound of general formula **(V.ii)**. When A represents a carbazolyl radical in which R^9 represents alkyl or a -COR^{15} group (case not shown in Diagram 3.8), the initial acylation stage is unnecessary and the last two stages of Diagram 3.8 allow the compounds of general formula **(V.ii)** to be obtained. Of course, the phenol or aniline functions resulting from the nature of the R^4, R^5, R^6, R^7 and R^8 substituents can lead a person skilled in the art to add to the stages represented in Diagram 3.8 protection stages (and, subsequently in the synthesis of the compounds of general formula **(I)**, deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis.

- when A represents a phenothiazinyl radical, the intermediates of general formula **(V.i)** and **(V.ii)** are accessible from methods in the literature: *J. Heterocyclic. Chem.* (1978), **15**, 175-176 and *Arzneimittel Forschung* (1962), **12**, 48.

Alternatively, the intermediates of general formula **(V.ii)** in which A represents a phenothiazinyl radical can be prepared according to a protocol which is slightly modified with respect to that described for the phenothiazinyl radical in *Arzneimittel Forschung* (1962), **12**, 48, which is summarized in Diagram 3.9 hereafter (see also the examples). The phenothiazine of general formula **(XXVI)** is protected using chloroacetyl chloride in order to produce the compound of general formula **(XXVII)**, which is then subjected to a Friedel-Crafts reaction (compound of general formula **(XVIII)** in a solvent such as carbon disulphide in the presence of aluminium chloride) in order to produce the compound of general formula **(XXVIII)**. During the last stage of the process, hydrolysis with HCl/acetic acid is accompanied by a halogen exchange and allows the chloroketone of general formula **(V.ii)** to be obtained. Of course, the phenol or aniline functions resulting from the nature of the R^4, R^5, R^6, R^7 and R^8 substituents can lead a person skilled in the art to add to the stages shown in Diagram 3.9 protection stages (and, subsequently in the synthesis of the compounds of general formula **(I)**, deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis.

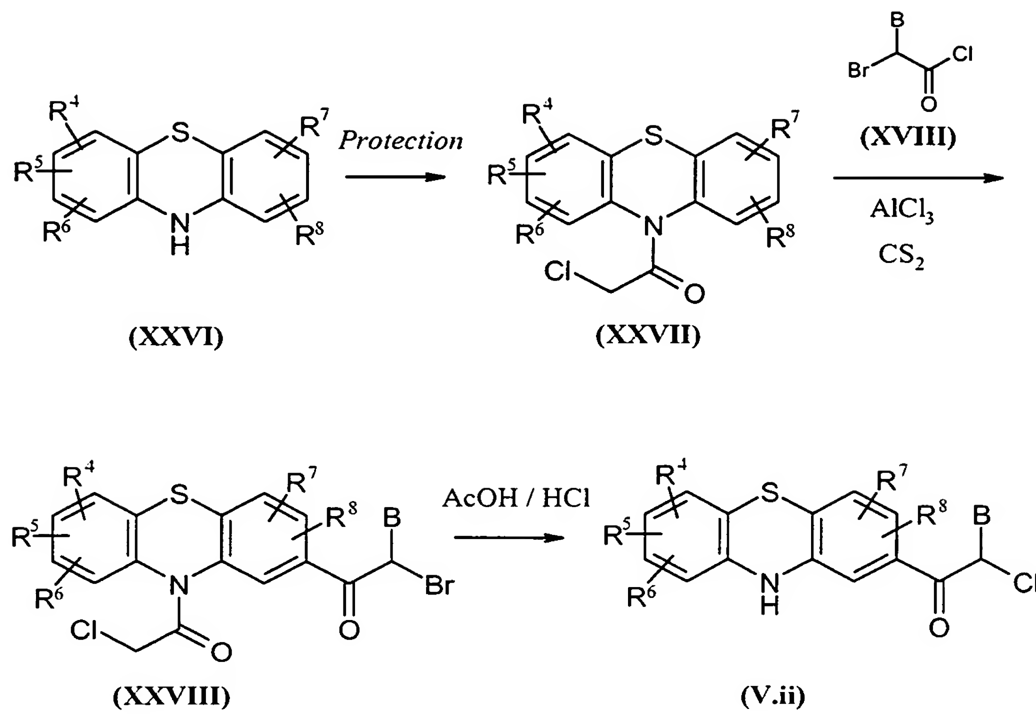


Diagram 3.9

- when A represents a phenylaminophenyl radical, the compounds of general formula **(V.i)** are accessible from methods in the literature such as for example *Chem. Commun.*, (1998), **15**, (6) 1509-1510 or *Chem Ber.*, (1986), **119**, 3165-3197, or similar methods which a person skilled in the art will have adapted.

For example, the intermediates of general formula **(V.i)a** and **(V.ii)a** in which A represents a phenylaminophenyl radical (which correspond to the corresponding compounds of general formula **(V.i)** and **(V.ii)** the aniline function of which has been acetylated), can be prepared according to a protocol which is slightly modified with respect to that described for the phenylaminophenyl radical in *Chem Ber.* (1986), **119**, 3165-3197. This protocol is summarized in Diagram 3.10 hereafter.

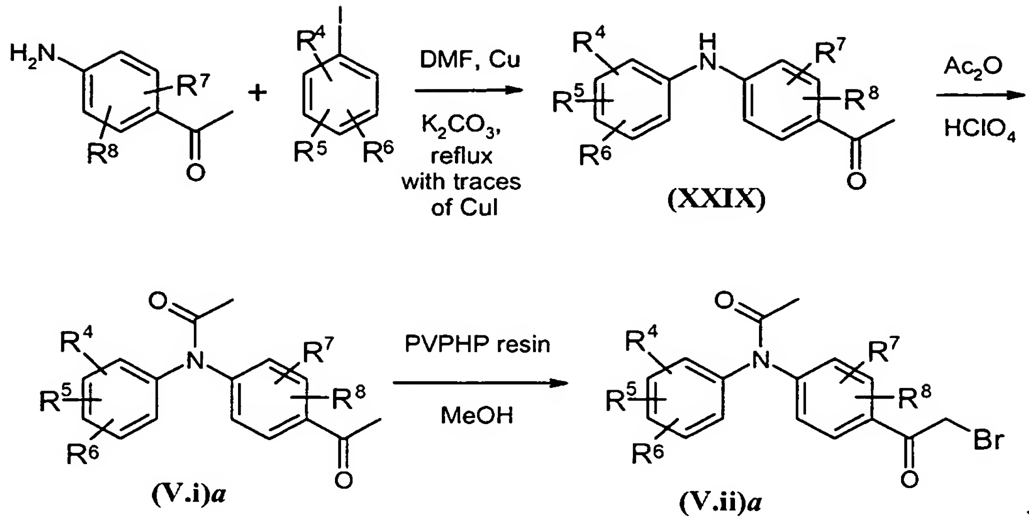


Diagram 3.10

In the case (shown in Diagram 3.10) where the R^9 radical of the compound of general formula **(I)** to be synthesized is a hydrogen atom or an acetyl group, the diphenylamine of general formula **(XXIX)** formed after the coupling reaction in the presence of CuI is protected by acetylation using, for example, acetic anhydride in order to produce the compound of general formula **(V.i)*a***. In the case (not shown in Diagram 3.10) where the R^9 radical of the compound of general formula **(I)** to be synthesized is not a hydrogen atom or an acetyl radical, the acetylation stage is replaced by a substitution stage of the aniline according to standard methods known to a person skilled in the art in order to produce the corresponding compound of general formula **(V.i)**. The compound of general formula **(V.i)*a*** (or **(V.i)**, in the case not shown in Diagram 3.10) is then subjected to a bromination reaction using a bromination resin, PVPHP resin *(Poly(VinylPyridinium Hydrobromide Perbromide)*, described in *J. Macromol. Sci. Chem.* (1977), **A11**, (3), 507-514, in order to produce the compound of general formula **(V.ii)*a*** (or **(V.ii)**, in the case not shown in Diagram 3.10). Of course, the phenol or aniline functions resulting from the nature of the R^4, R^5, R^6, R^7 and R^8 substituents can lead a person skilled in the art to add to the stages shown in Diagram 3.10 protection stages (and, subsequently in the synthesis of the compounds of general formula **(I)**, deprotection stages) of these functions so that they do not interfere with the remainder of the chemical synthesis. The deprotection of the acetylated aniline function will be carried out in principle during the last stage of the synthesis of the compounds of general formula **(I)**.

- when A represents a benzopyran or benzofuran radical as defined in general formula **(I)** with R^{32} representing a hydrogen atom, the intermediates of general formula **(V.i)** and **(V.ii)** are accessible by the methods illustrated in Diagram 3.11 below.

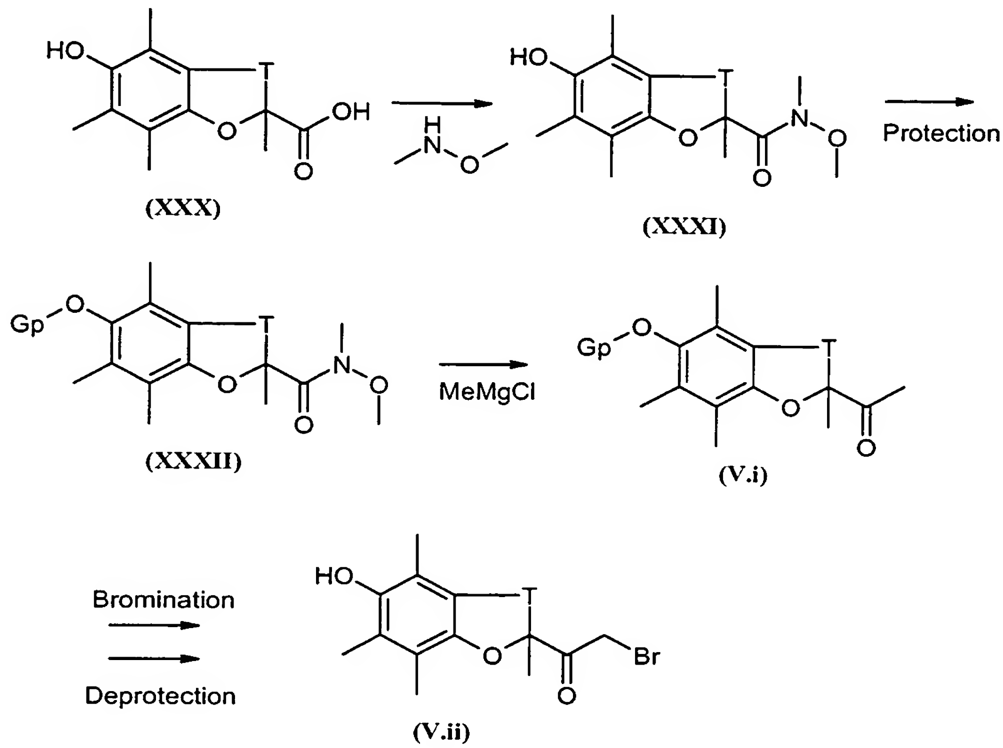


Diagram 3.11

The compounds of general formulae **(V.i)** and **(V.ii)**, according to Diagram 3.11, in which T is as defined above and Gp = protective group, are prepared from the acids of general formula **(XXX)**. The acids of general formula **(XXX)** are subjected to coupling with N,O-dimethylhydroxylamine (*Syn. Commun.* (1995), **25**, (8), 1255; *Tetrahedron Lett.* (1999), **40**, (3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazol, in order to produce the intermediates of general formula **(XXXI)**. The protection of the phenol function in the form of a benzylated or *tert*-butyldimethylsilylated derivative or by other protective groups (Gp) known to a person skilled in the art is then carried out in order to produce the compounds of general formula **(XXXII)**. The compounds of general formula **(V.i)** are prepared from the compounds of general formula **(XXXII)** by a substitution reaction with a Grignard reagent, MeMgCl (*J. Het. Chem.* (1990), **27**, 1709-1712) or with MeLi (*J. Med. Chem.* (1992), **35**, 13). The bromoacetophenones of general

formula **(V.ii)** are now accessible from the acetophenone of general formula **(V.i)** under previously described conditions.

Alternatively, the compound of general formula **(V.ii)** in which R^{32} represents a hydrogen atom or an alkyl radical can be prepared according to a process in only 3 stages (cf. Diagram 3.12 – see also the examples). In this process, the bromination in the last stage of the compound of general formula **(V.i)** in order to produce the compound of general formula **(V.ii)** will preferably be carried out according to *J. Am. Chem. Soc.* (1999), **121**, 24.

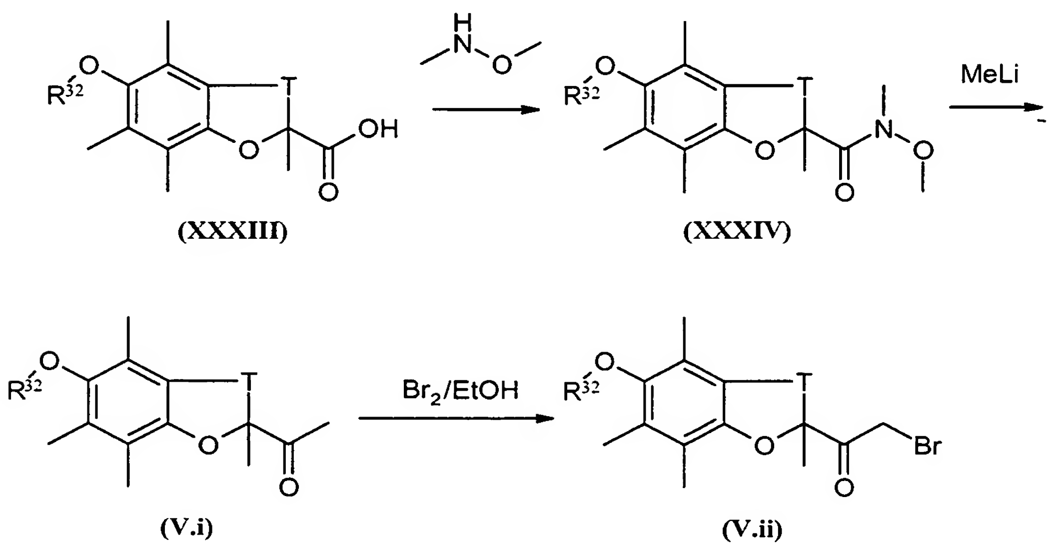
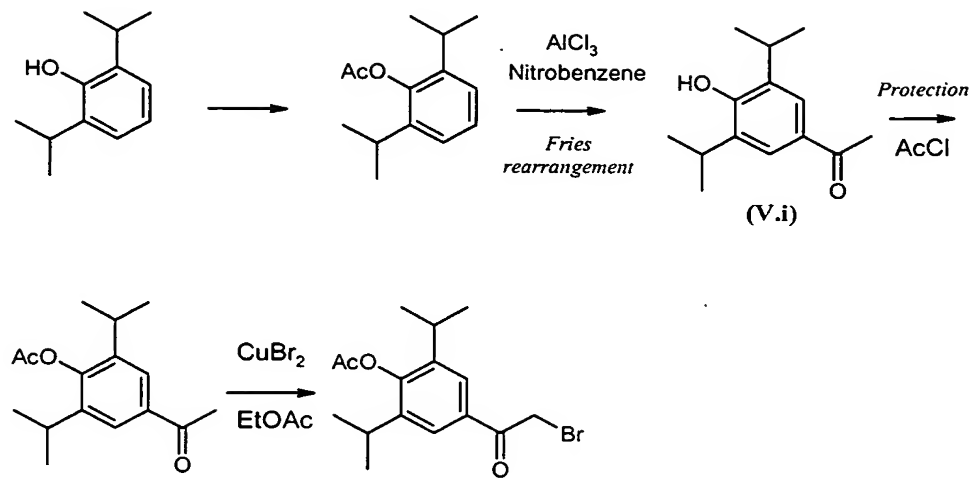


Diagram 3.12

When A represents a substituted phenol radical, it can be necessary to use intermediates of general formula **(V.ii)** as defined previously the phenol function of which has been acetylated (hereafter designated as compounds of general formula **(V.ii)*b***). In particular:

- when A represents a 4-hydroxy-3,5-diisopropylphenyl radical, the homologous α-bromoketonic derivatives of the compound of formula **(V.ii)** the phenol function of which is protected by an acetyl radical can be prepared as summarized in Diagram 3.13 hereafter.



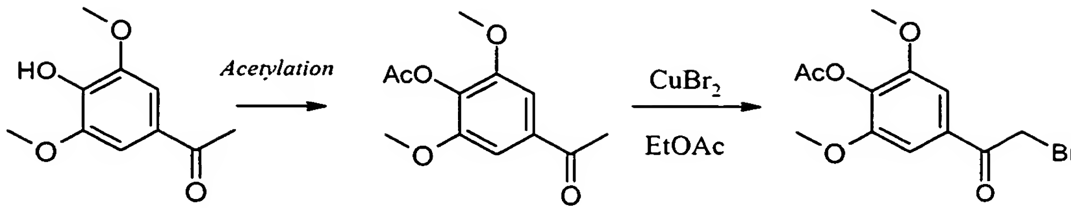
(V.i)

(V.i)*b* **(V.ii)*b***

Diagram 3.13

2,6-diisopropylphenol is acetylated according to methods known to a person skilled in the art, for example by reacting it with acetic acid in the presence of trifluoroacetic acid anhydride or with acetyl chloride in the presence of a base such as for example K_2CO_3. The acetylated homologue of 2,6-diisopropylphenol is then subjected to a Fries rearrangement in the presence of aluminium chloride in a solvent such as nitrobenzene in order to produce the compound of formula **(V.i)**. Then the compound of formula **(V.i)** is acetylated in order to produce the compound of formula **(V.i)*b***. Bromination is then carried out with $CuBr_2$ as previously described in order to produce the compound of formula **(V.ii)*b***. The deprotection stage to release the phenol function will occur subsequently in the synthesis of the compounds of general formula **(I)** (at the time considered most appropriate by a person skilled in the art).

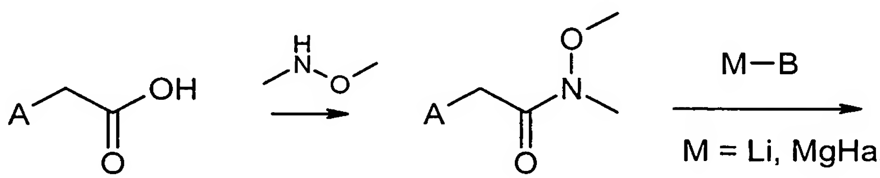
- when A represents a radical of dimethoxyphenol type, the compounds of general formula **(V.ii)*b*** can be prepared in a similar fashion to the synthesis described for the compound of formula **(V.ii)*b*** derived from 2,6-diisopropylphenol, optionally with a few minor modifications within the scope of a person skilled in the art. For example, when A represents the 3,5-dimethoxy-4-hydroxyphenyl radical, the corresponding α-bromoketonic derivative of formula **(V.ii)*b*** can be prepared, for example, as indicated in Diagram 3.13 from the commercial compound of formula **(XXXV)**:



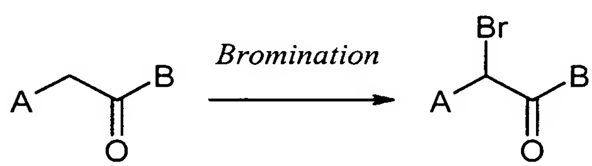
(XXXV) (V.i)*b* (V.ii)*b*

Diagram 3.14

The compounds of general formula **(V.ii)**$_2$ in which A and B are as defined previously can be prepared according to the method summarized in Diagram 3.15 hereafter.



(XXXVI) (XXXVII)



(V.i)$_2$ (V.ii)$_2$

Diagram 3.15

The acids of general formula **(XXXVI)** are subjected to coupling with N,O-dimethylhydroxylamine (*Syn. Commun.* (1995), **25**, (8), 1255; *Tetrahedron Lett.* (1999), **40**, (3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazol, in order to produce the intermediates of general formula **(XXXVII)**. The compounds of general formula **(V.i)**$_2$ are prepared from the compounds of general formula **(XXXVII)** by a substitution reaction with lithium compound or magnesium compound derivatives of general formula B-M in which M represents Li or MgHal (Hal = I, Br or Cl) in solvents such as ether or anhydrous tetrahydrofuran. The α-bromo- or α-chloroketones of general formula **(V.ii)**$_2$ can now be accessed from the ketones of general formula **(V.i)**$_2$ under the conditions previously described.

Moreover, the non commercial α-halogenoketonic derivatives of general formula **(V.vii)** are accessible from methods in the literature. In particular, they can be obtained according to a procedure summarized in Diagram 3.16.

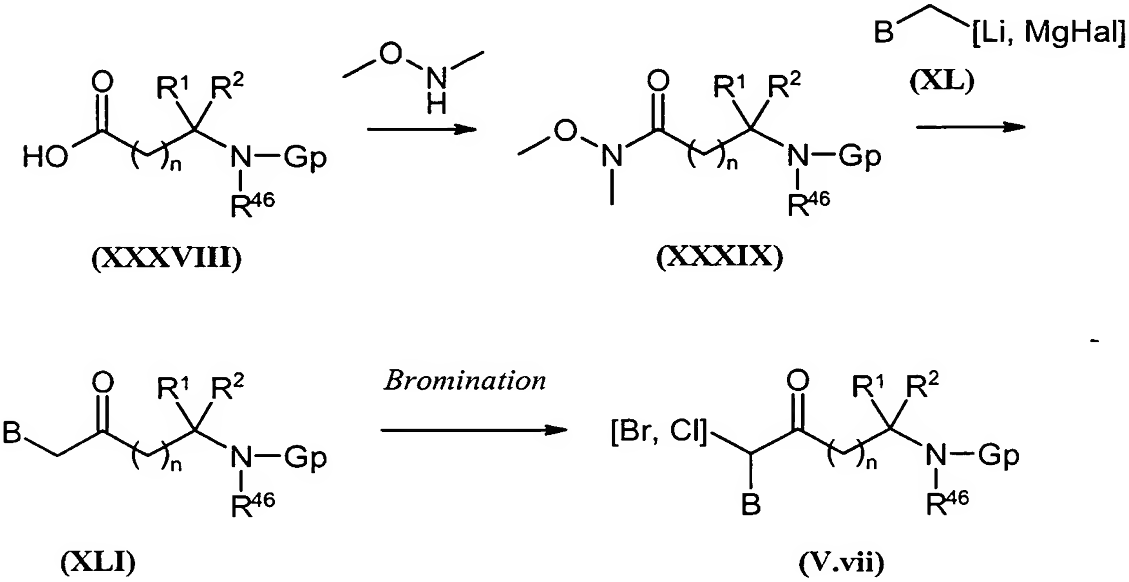


Diagram 3.16

The protected amino acids of general formula **(XXXVIII)** are obtained by protection of the corresponding amino acids by a group of carbamate type according to methods known to a person skilled in the art. The acids of general formula **(XXXVIII)** are then subjected to coupling with N,O-dimethylhydroxylamine (*Syn. Commun.* (1995), **25**, (8), 1255; *Tetrahedron Lett.* (1999), **40**, (3), 411-414) in a solvent such as dimethylformamide or dichloromethane, in the presence of a base such as triethylamine with dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and hydroxybenzotriazole, in order to produce the intermediates of general formula **(XXXIX).** The compounds of general formula **(XLI)** are prepared from the compounds of general formula **(XXXIX)** by a substitution reaction with lithium compound or magnesium compound derivatives of general formula **(XL)** (in which Hal = I, Br or Cl) in solvents such as ether or anhydrous tetrahydrofuran. The bromo or chloroacetophenones of general formula **(V.vii)** are now accessible from the acetophenone of general formula **(XLI)** under the conditions previously described.

Alternatively, a person skilled in the art can also use or adapt the syntheses described in *Angew. Chem. Int.* (1998), **37** (10), 411-414, *Liebigs Ann. Chem.* (1995), 1217 or *Chem. Pharm. Bull.* (1981), **29**(11), 3249-3255.

Preparation of the acid derivatives of general formula (V.iii)

The acid derivatives of general formula **(V.iii)** can be obtained, Diagram 3.17, directly by reaction of the commercial amino acid of general formula **(V.vi)** with the compounds of (ar)alkylchloroformate or di(ar)alkylcarbonate type (Δ represents an alkyl or benzyl radical) under standard conditions known to a person skilled in the art.

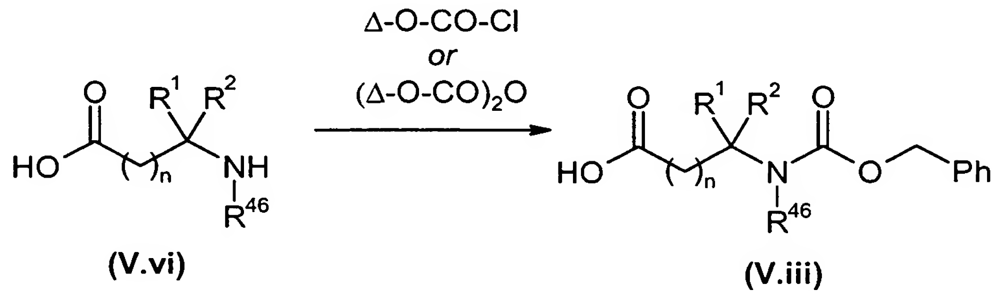


Diagram 3.17

Preparation of the compounds of general formula (V.v)

The thiocarboxamides of general formula **(V.v)** can be obtained in three stages starting from the compounds of general formula **(V.vi)** as indicated in the Diagram 3.18 below. The amine function of the amino acid of general formula **(V.vi)** is firstly protected under standard conditions with tBu-O-CO-Cl or $(tBu\text{-}O\text{-}CO)_2O$ (or other protective groups known to a person skilled in the art), then the intermediate obtained is converted to its corresponding amide by methods described in the literature (cf. for example, *J. Chem. Soc., Perkin Trans. 1*, (1998), **20** , 3479-3484 or the PCT Patent Application WO 99/09829). Finally, the carboxamide is converted to the thiocarboxamide of general formula **(V.v)**, for example by reaction with Lawesson reagent in a solvent such as dioxane or tetrahydrofuran at a temperature preferably comprised between ambient temperature and the reflux temperature of the mixture, or also using $(P_2S_5)_2$ under standard conditions for a person skilled in the art.

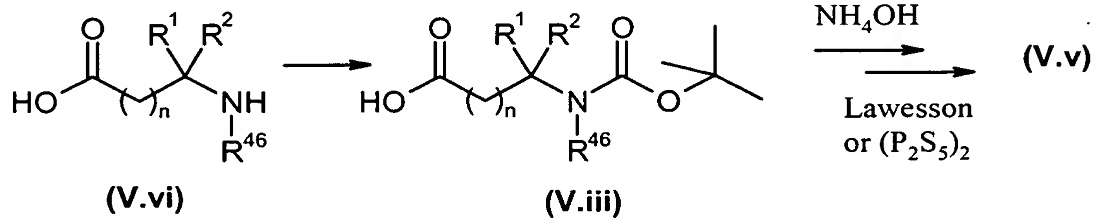


Diagram 3.18

Alternatively, the thiocarboxamides of general formula **(V.v)** can also be obtained, Diagram 3.19, by the addition of H_2S on the corresponding cyano derivatives of general formula **(V.x)** under standard conditions known to a person skilled in the art.

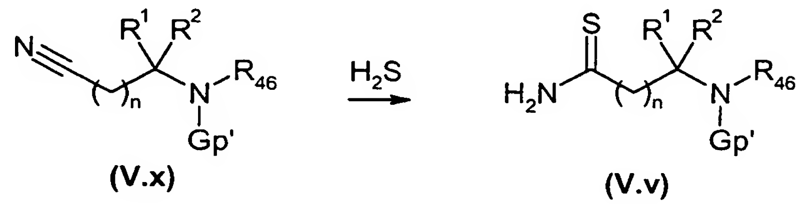


Diagram 3.19

Preparation of the acids of general formula (VI)

Preparation of the acid derivatives of thiazoles of general formula (VI)

The acids of general formula **(VI)** derived from thiazoles can be prepared according to the procedures represented in Diagram 4.1 below.

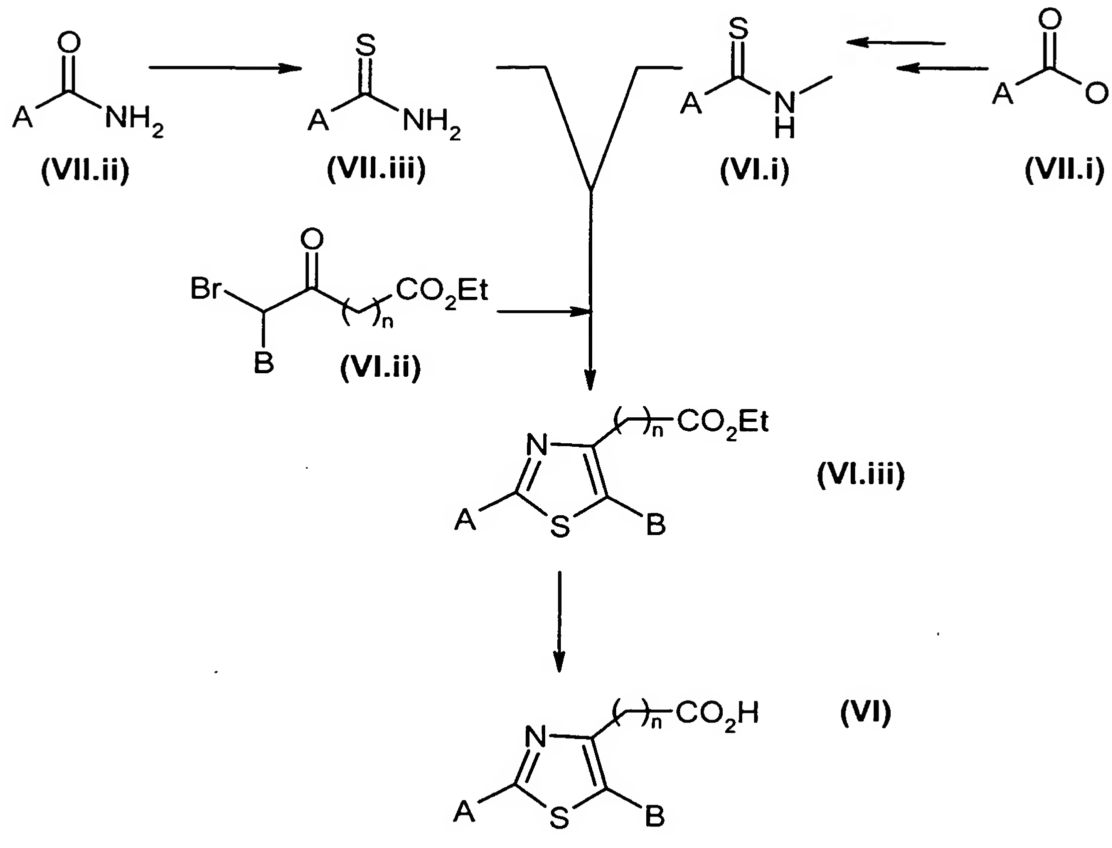


Diagram 4.1

The carboxamides of general formula **(VII.ii)** are treated under standard conditions in order to produce the thiocarboxamide of general formula **(VII.iii)**, for example by Lawesson reagent or also using $(P_2S_5)_2$ under standard conditions for a person skilled in the art. Alternatively the acid of general formula **(VII.i)** is activated by the action of 1.1'-carbonyldiimidazole then treated with methylamine in an aprotic polar solvent such as for example tetrahydrofuran. The carboxamide intermediate obtained is converted to the thiocarboxamide of general formula **(VI.i)** under standard conditions, for example using Lawesson reagent or also using $(P_2S_5)_2$ under standard conditions for a person skilled in the art. The thiocarboxamide of general formula **(VII.iii)** or **(VI.i)** is then reacted with the compound of general formula **(VI.ii)**, for example while heating at reflux in a solvent such as benzene, dioxane or dimethylformamide. The ester of general formula **(VI.iii)** obtained can then be saponified by the action of a base such as for example potash in alcoholic medium or LiOH in tetrahydrofuran in order to produce the acid of general formula **(VI)**.

Preparation of the acid derivatives of oxazoles of general formula (VI)

The acids of general formula **(VI)** derived from oxazoles can be prepared according to a procedure represented in Diagram 4.2 below.

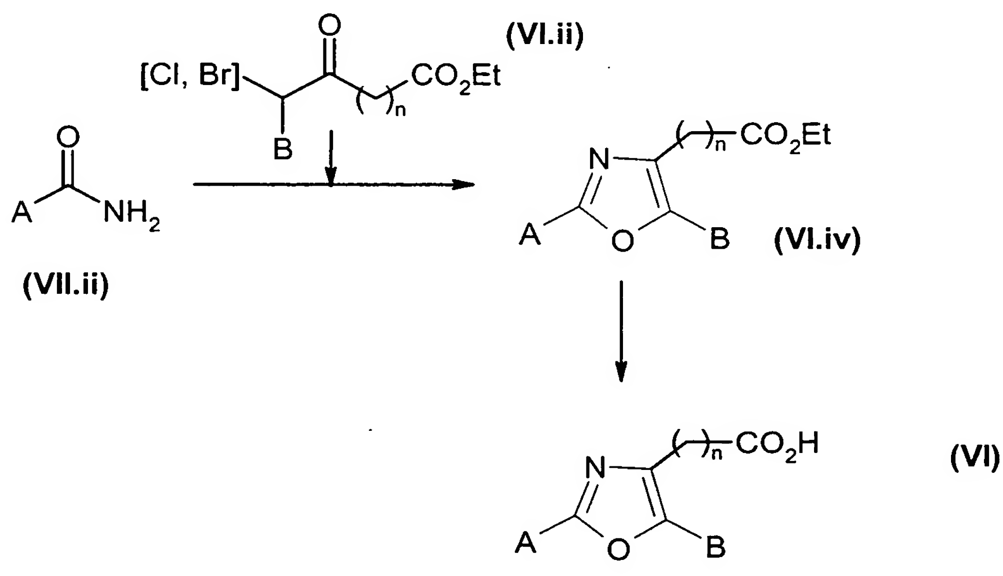


Diagram 4.2

The carboxamides of general formula **(VII.ii)** are reacted with the compound of general formula **(VI.ii)** while heating, for example at reflux, in the absence or in the presence of a solvent such as dimethylformamide. The ester of general formula **(VI.iv)** obtained can then be saponified by the action of a base such as for example potash in alcoholic

medium or LiOH in tetrahydrofuran in order to produce the acid of general formula (VI).

Preparation of the acid derivatives of isoxazolines of general formula (VI)

The acid derivatives of isoxazolines of general formula (VI), used in the preparation of compounds of general formula $(I)_4$, can be prepared according to a procedure represented in Diagram 4.3 below.

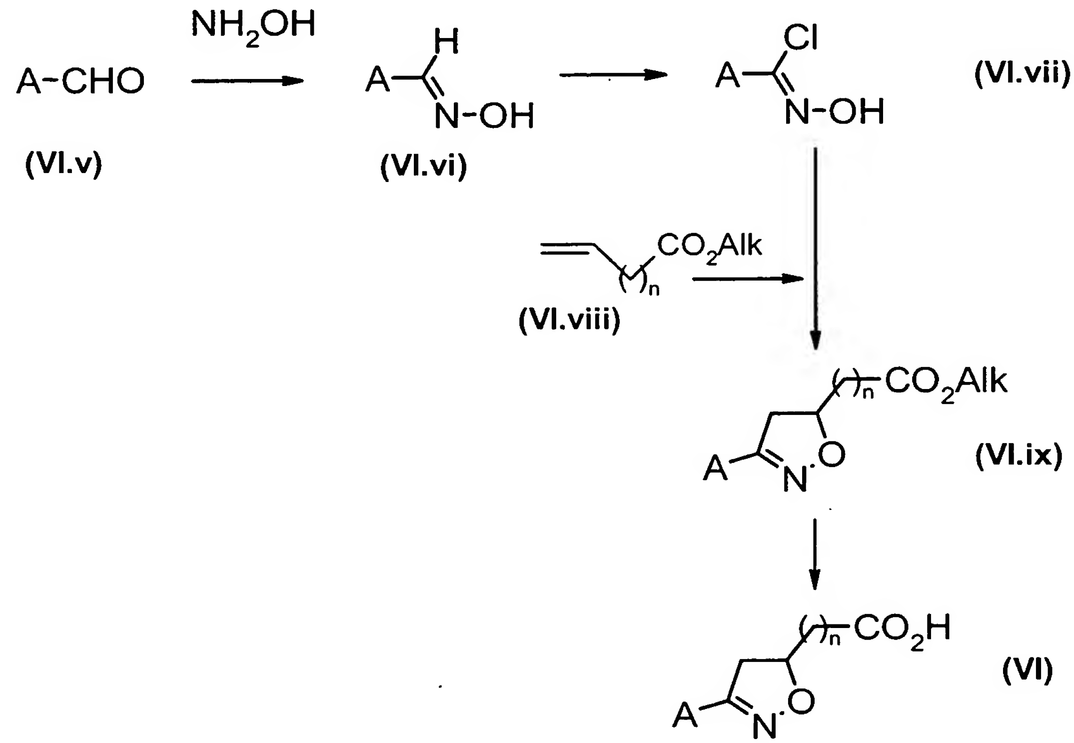


Diagram 4.3

The acids of general formula (VI) derived from isoxazolines can be prepared as follows: the commercial aldehydes of general formula **(VI.v)** are reacted with hydroxylamine hydrochloride. The oxime of general formula **(VI.vi)** thus obtained is activated in the form of oxime chloride, of general formula **(VI.vii)**, by reaction with N-chlorosuccinimide in DMF before reacting with the esters of general formula **(VI.viii)** (in which Alk represents an alkyl radical) in order to produce the isoxazoline derivatives according to an experimental protocol described in the literature (*Tetrahedron Lett.*, 1996, **37** (26), 4455; *J. Med. Chem.*, 1997, **40**, 50-60 and 2064-2084). Saponification of the isoxazolines of general formula **(VI.ix)** is then carried out in a standard fashion (for example by the action of KOH in an alcoholic solvent or

LiOH in a solvent such as tetrahydrofuran) in order to produce the acid derivative of general formula **(VI)**.

The non-commercial unsaturated esters of general formula **(VI.x)** can be prepared according to the methods described in the literature (*J. Med. Chem.*, 1987, **30**, 193; *J. Org. Chem.*, 1980, **45**, 5017).

Preparation of the thiazoles and oxazoles of general formula (VII)

General outline

The acids of general formula **(VII.i)**, Diagram 5.1, are converted to the corresponding carboxamides of general formula **(VII.ii)** by methods described in the literature (cf. for example, *J. Chem. Soc., Perkin Trans. 1*, (1998), **20** , 3479-3484 or the PCT Patent Application WO 99/09829). The compounds of general formula **(VII)** can then be obtained in a standard fashion according to the procedures represented in Diagrams 5.2 and 5.3 (thiazoles) and Diagram 5.4 (oxazoles) hereafter.

This synthesis route is useful for then preparing the compounds corresponding to general sub-formulae **(I)**$_1$ and **(I)**$_3$.

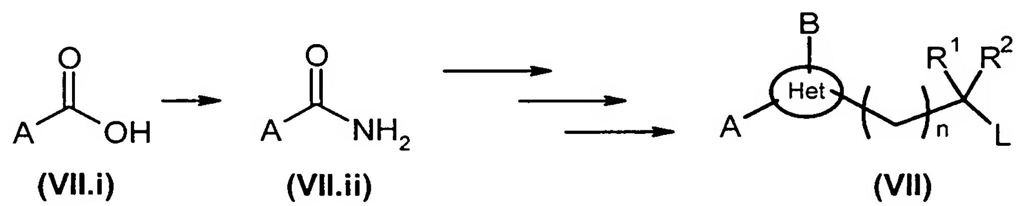


Diagram 5.1

Obtaining the thiazoles of general formula (VII)

When R^1 and R^2 both represent H, the thiazoles of general formula **(VII)** intended for the preparation of compounds of general formula **(I)**$_3$ can be prepared according to the method summarized in Diagram 5.2. The carboxamide of general formula **(VII.ii)** is converted to the corresponding thiocarboxamide of general formula **(VII.iii)** in the presence of Lawesson reagent in a solvent such as dioxane or benzene at a temperature preferably comprised between ambient temperature and that of reflux of the mixture. The thiocarboxamide of general formula **(VII.iii)** is then treated with the α-halogenoketoester of general formula **(VII.iv)** in which Alk represents an alkyl radical (for example methyl, ethyl or *tert*-butyl), in order to produce the ester of general formula **(VII.v)**, which is reduced to the corresponding alcohol of general formula **(VII.vi)**, for example by the action of lithium aluminium hydride or

diisobutylaluminium hydride in a solvent such as tetrahydrofuran. This latter can then be converted to a halogenated derivative of general formula **(VII)** according to the methods known to a person skilled in the art, for example, in the case of a brominated derivative (L = Br), by reaction with CBr_4 in the presence of triphenylphosphine in dichloromethane at ambient temperature.

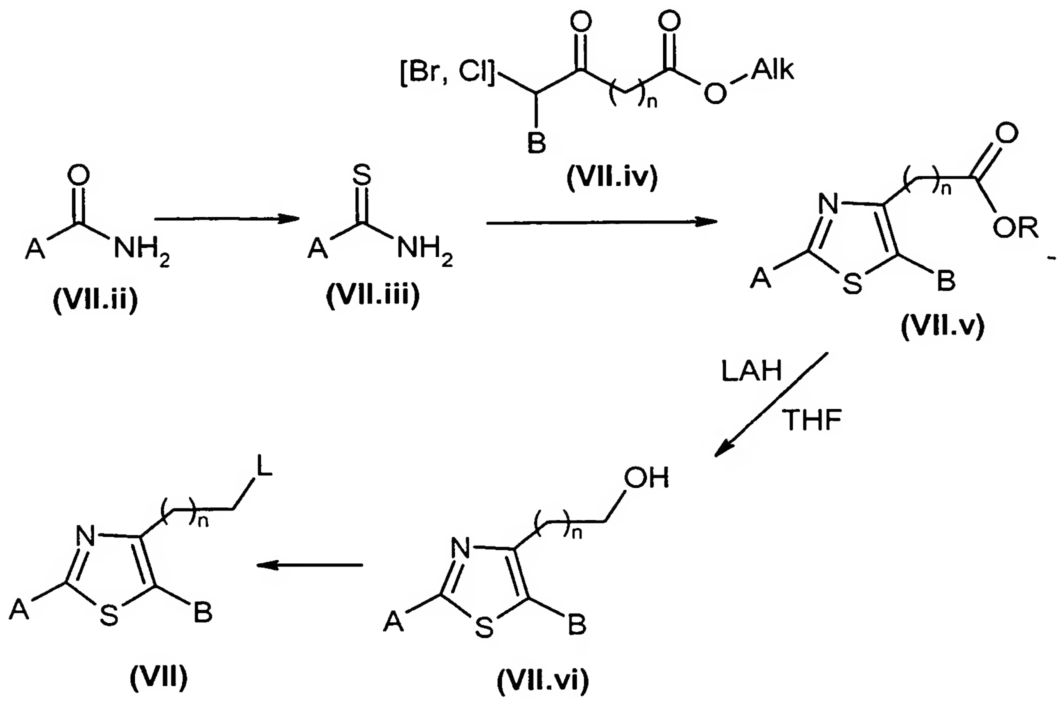


Diagram 5.2

The thiazoles of general formula **(VII)** intended for the preparation of compounds of general formula $(\mathbf{I})_1$ can be prepared according to the method summarized in Diagram 5.3. The cyano derivative of general formula **(VII.vii)** in which Gp' is a protective group for an alcohol function (for example a benzyl or –CO-ρ group in which ρ represents alkyl, for example methyl or *tert*-butyl) is converted to the corresponding thiocarboxamide of general formula **(VII.viii)** by the action of H_2S in a solvent such as ethanol in the presence of triethanolamine at a temperature preferably comprised between ambient temperature and that of reflux of the mixture. The thiocarboxamide of general formula **(VII.viii)** is then treated with the α-halogenoketone of general formula **(VII.ix)** in order to produce the compound of general formula **(VII.x)**, which is deprotected in order to produce the corresponding alcohol of general formula **(VII.xi)** according to methods known to a person skilled in the art (for example when Gp' is a protective group of acetate type, this is removed *in situ* by the action of an aqueous solution of sodium carbonate). This latter can then be converted to a halogenated

derivative of general formula **(VII)** according to the methods known to a person skilled in the art, for example, in the case of a brominated derivative (L = Br), by reaction with CBr_4 in the presence of triphenylphosphine in dichloromethane at ambient temperature.

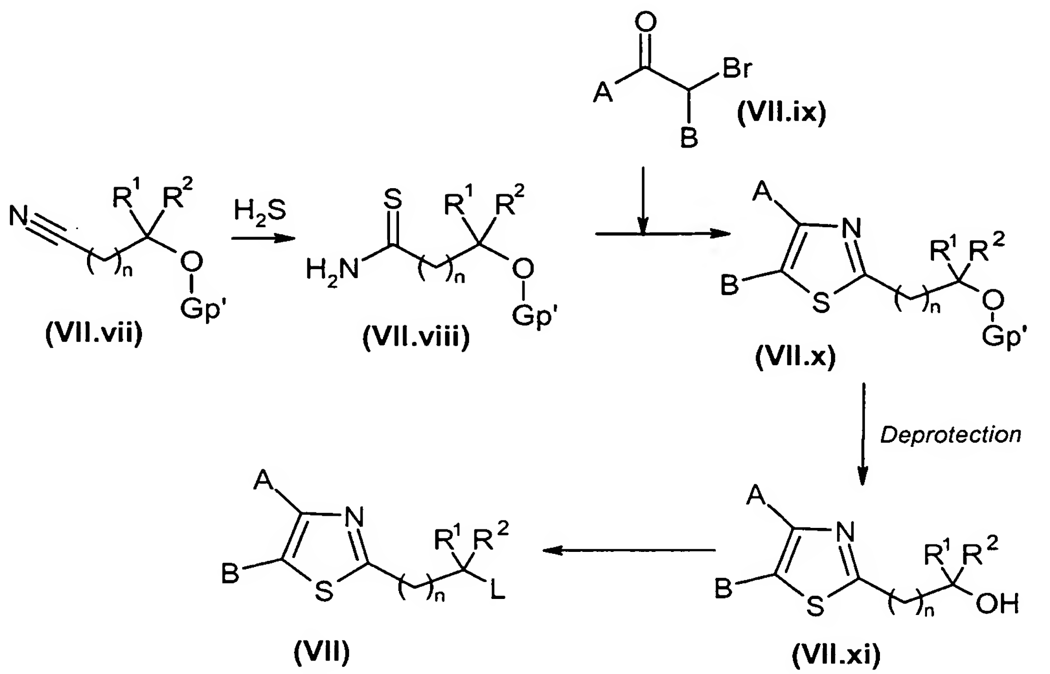


Diagram 5.3

Obtaining the oxazoles of general formula (VII)

When R^1 and R^2 both represent H, the oxazoles of general formula **(VII)** intended for the preparation of compounds of general formula $(I)_3$ can be prepared according to the method summarized in Diagram 5.4. The carboxamide of general formula **(VII.ii)** is treated with the α-halogenoketoester of general formula **(VII.iv)** in which Alk represents an alkyl radical (for example methyl, ethyl or *tert*-butyl), in order to produce the ester/acid of general formula **(VII.xii)**. This latter is reduced to the corresponding alcohol of general formula **(VII.xiii)**, for example by the action of lithium and aluminium hydride or diisobutylaluminium hydride in a solvent such as tetrahydrofuran when one starts from the ester or by the action of diborane in tetrahydrofuran when one starts from the acid. This latter can then be converted to a halogenated derivative of general formula **(VII)** according to methods known to a person skilled in the art, for example, in the case of a brominated derivative (L = Br), by reaction with CBr_4 in the presence of triphenylphosphine in dichloromethane at ambient temperature.

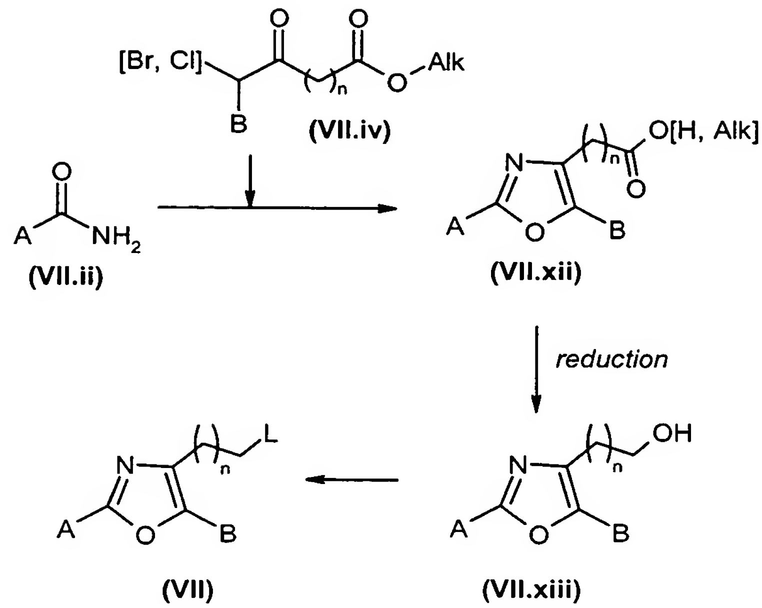


Diagram 5.4

Preparation of the acids of general formula (VII.i)

The non-commercial acids of general formula **(VII.i)** are accessible from methods in the literature. In particular:

- when A represents a phenothiazinyl radical, the acids of general formula **(VII.i)** are accessible from methods in the literature such as for example *J. Med. Chem.* (1992), **35**, 716-724, *J. Med. Chem.* (1998), **41**, 148 –156; *Synthesis* (1988) 215-217; or *J. Chem. Soc. Perkin. Trans. 1* (1998), 351-354;

- when A represents an indolinyl radical, the acids of general formula **(VII.i)** are accessible from methods in the literature such as for example *J. Het. Chem.* (1993), **30**, 1133-1136 or *Tetrahedron* (1967), **23**, 3823;

- when A represents a phenylaminophenyl radical, the acids of general formula **(VII.i)** are accessible from methods in the literature such as for example *J. Amer. Chem Soc.* (1940), **62**, 3208; *Zh. Obshch. Khim.* (1953), **23**, 121-122 or *J. Org. Chem.* (1974), 1239-1243;

- when A represents a carbazolyl radical, the acids of general formula **(VII.i)** are accessible from methods in the literature such as for example *J. Amer. Chem Soc.*, (1941), **63**, 1553-1555; *J. Chem. Soc.* (1934), 1142-1144; *J. Chem. Soc.* (1945), 945-956; or *Can. J. Chem. Soc.* (1982), 945-956; and

- when A represents a radical of 4-(4-hydroxyphenyl)-phenyl type, reference will be made for example to the following publication: *Synthesis* (1993) 788-790.

Preparation of the compounds of general formula (VIII)

When R^1 and R^2 both represent H, the protected amino acids of general formula **(VIII)** are either commercial, or obtained by protection of commercial amino acids by a group of carbamate type according to the methods known to a person skilled in the art.

When at least one of R^1 and R^2 is not H, and n = 0, the protected amino acids of general formula **(VIII)** are obtained in one stage, Diagram 6.1, by alkylation, in a solvent such as tetrahydrofuran and at low temperature, of commercial compound of general formula **(VIII.i)** using 3 equivalents of butyllithium and approximately one equivalent of the halogenated derivative of general formula **(VIII.ii)** in which R^1 represents a radical of alkyl, cycloalkyl, cycloalkylalkyl or arylalkyl type and Hal a halogen atom. Depending on the case, a second alkylation (not represented in Diagram 6.1) can be carried out in a similar fashion, thus allowing the compounds of general formula **(VIII)** to be obtained in which neither R^1 nor R^2 represents H.

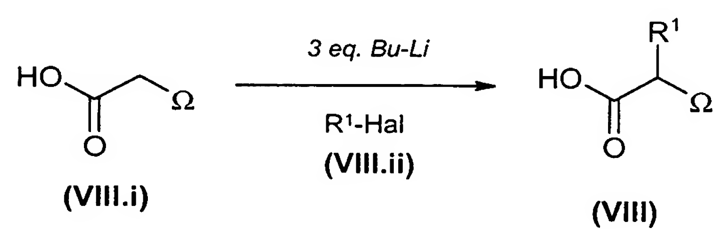


Diagram 6.1

Preparation of the imidazoles, thiazoles and oxazoles of general formula (IX)

The preparation of the intermediates of general formula **(IX)** is described in the Patent Application WO 98/58934 (cf. in particular pages 10 to 50 and the examples of this document) or carried out by analogy from commercial starting products

Preparation of the protected alcohols of general formula (X)

Preparation of the compounds of general formula (X) derived from imidazoles

The acid of general formula **(X.i)** is successively treated, Diagram 8.1, with Cs_2CO_3, the compound of general formula **(V.ii)** and with NH_4OAc, in order to produce the compound of general formula **(X)**. The reaction conditions are similar to those described above for this type of synthesis.

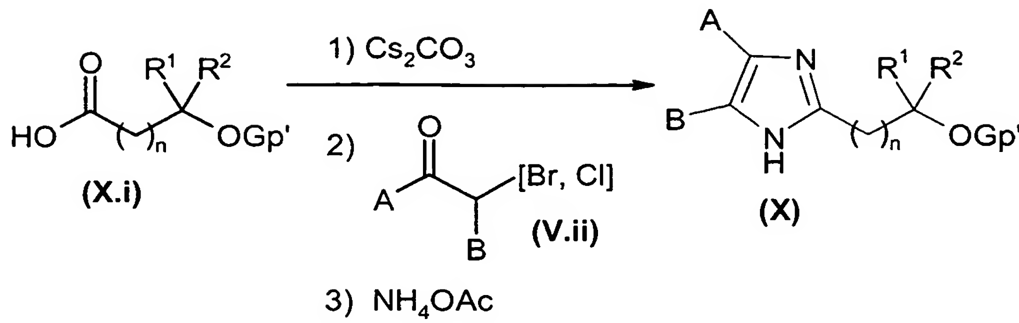


Diagram 8.1

Preparation of the compounds of general formula (X) derived from thiazoles

The cyano derivative of general formula **(X.ii)** is treated, Diagram 8.2, with H_2S in order to produce the thiocarboxamide of general formula **(X.iii)**, which, condensed with the compound of general formula **(V.ii)**, allows the compound of general formula **(X)** to be obtained. The reaction conditions are similar to those described above (Diagram 5.3) for this type of synthesis.

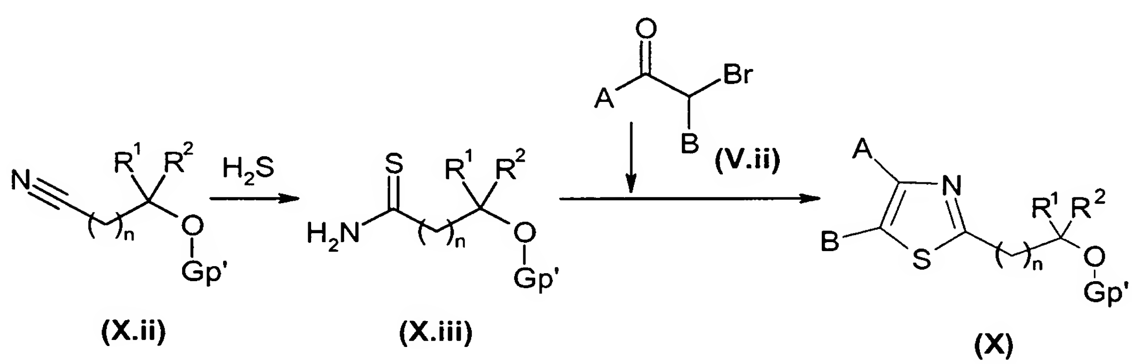


Diagram 8.2

Preparation of the acids of general formula (XXXVI)

The non commercial acids of general formula **(XXXVI)** are accessible from methods in the literature or similar methods adapted by a person skilled in the art. In particular:

- when A represents a phenothiazinyl radical, the acids of general formula **(XXXVI)** are accessible from methods in the literature: *J. Org. Chem.*, (1956), **21**, 1006; *Chem. Abstr.*, **89**, 180029 and *Arzneimittel Forschung* (1969), **19**, 1193.
- when A represents a diphenylamine radical, the acids of general formula **(XXXVI)** can be accessed from methods in the literature: *Chem Ber.*, (1986), **119**, 3165-3197 ;

J. Heterocyclic. Chem. (1982), **15**, 1557-1559 ; *Chem. Abstr.,* (1968), **68**, 68730x ; or by adaptation of these methods by a person skilled in the art;

- when A represents a radical of 4-(4-hydroxyphenyl)-phenyl type, the acids of general formula **(XXXVI)** can be accessed from methods in the literature such as for example *Tetrahedron Lett.* (1968), 4739 or *J. Chem. Soc.* (1961), 2898.
- when A represents a carbazolyl radical, the acids of general formula **(XXXVI)** can be accessed from methods in the literature such as for example *J. Amer. Chem.*, (1946), **68**, 2104 or *J. Het. Chem* (1975), **12**, 547-549.
- when A represents a radical of benzopyrane or benzofurane type, the acids of general formula **(XXXVI)** can be accessed by the methods in the literature such as for example *Syn. Commun.* (1982), **12**(8), 57-66; *J. Med. Chem.* (1995), **38**(15), 2880-2886; or *Helv. Chim. Acta* . (1978), **61**, 837-843.
- when A represents an indolinyl or tetrahydroquinolyl radical, the acids of general formula **(XXXVI)** can be accessed from methods in the literature such as for example *J. Med. Chem.* (1997), **40**, (7), 1049-1062; *Bioorg. Med. Chem. Lett.* (1997), 1519-1524; *Chem. Abstr.* (1968), **69**, 43814k; or *Chem. Abstr.* (1966), **66**, 17538c.

Of course, the phenol, amine or aniline functions resulting from the nature of the substituents on the A radical of the compounds of general formula **(XXXVI)** can lead a person skilled in the art to add protection/deprotection stages of these functions to the stages described so that they do not interfere with the rest of the chemical synthesis.

Unless defined otherwise, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Likewise, all publications, patent applications, all patents and all other references mentioned here are incorporated by way of reference.

The following examples are presented to illustrate the above procedures and must in no case be considered as limiting the scope of the invention.

EXAMPLES

Example 1: 4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine:

This product is obtained according to the procedure described in the PCT Patent Application WO 98/58934. Alternatively, it can also be prepared according to the method described below.

1.1) *N-Boc-sarcosinamide:*

15.0 g (0.120 mol) of sarcosinamide hydrochloride (N-Me-Gly-NH_2.HCl) is dissolved in dichloromethane containing 46.2 ml (0.265 mol) of diisopropylethylamine. The mixture is cooled down to 0 °C then Boc-O-Boc (28.8 g; 0.132 mol) is added in fractions and the mixture is stirred overnight at ambient temperature. The reaction medium is then poured into ice-cooled water followed by extraction with dichloromethane. The organic phase is washed successively with a 10% aqueous solution of sodium bicarbonate and with water, then finally with a saturated solution of sodium chloride. The organic phase is then dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from diisopropyl ether in order to produce a white solid with a yield of 72%. Melting point: 103 °C.

1.2) *2-{[(1,1-dimethylethoxy)carbonyl]methyl}amino-ethanethioamide:*

16.0 g (0.085 mol) of intermediate 1.1 is dissolved in dimethoxyethane (500 ml) and the solution obtained is cooled down to 5 °C. Sodium bicarbonate (28.5 g; 0.34 mol) then, in small portions, $(P_2S_5)_2$ (38.76 g; 0.17 mol) are added. The reaction medium is allowed to return to ambient temperature under stirring over 24 hours. After evaporation of the solvents under vacuum, a 10% aqueous solution of sodium bicarbonate is added to the residue and the solution is extracted using ethyl acetate. The organic phase is washed successively with a 10% aqueous solution of sodium bicarbonate and with water, then finally with a saturated solution of sodium chloride. The organic phase is then dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from ether in order to produce a white solid with a yield of 65%. Melting point: 150-151 °C.

1.3) *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-[(1,1-dimethylethoxy)-carbonyl]-N-methyl-2-thiazolemethanamine:*

Intermediate 1.2 (4.3 g; 2.11 mmol) and bromo-1-(3,5-di*tert*-butyl-4-hydroxyphenyl)ethanone (6,9g; 2,11 mmol) are dissolved in benzene (75 ml) under an argon atmosphere, then the mixture is stirred at ambient temperature for 12 hours. The reaction medium is heated under reflux for 4 hours. After evaporation of the solvents, the residue is diluted with dichloromethane and washed with a saturated solution of NaCl. The organic phase is separated, dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 20% ethyl acetate in heptane) in the form of an oil which crystallizes very slowly in a refrigerator with a yield of 28%. Melting point: 126.5-127.3 °C.

1.4) *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine:*

2.3 ml (29 mmol) of trifluoroacetic acid is added dropwise, at 0 °C to a solution of 2.5 g (5.8 mmol) of intermediate 1.3 and 2 ml (1.6 mmol) of triethylsilane in 50 ml of dichloromethane. After stirring for one hour, the reaction mixture is concentrated under vacuum and the residue is diluted in 100 ml of ethyl acetate and 50 ml of a saturated solution of $NaHCO_3$. After stirring and decantation, the organic phase is dried over magnesium sulphate, filtered and concentrated under vacuum. The residue is taken up in heptane in order to produce, after drying, a white solid with a yield of 73%. Melting point: 136 °C.

1.5 *4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-2-thiazolemethanamine hydrochloride:*

2.0 g (0.602 mmol) of intermediate 1.4 is dissolved in anhydrous ether. The solution is cooled down to 0 °C then 18 ml (1.81 mmol) of a 1*N* solution of HCl in ether is added dropwise. The mixture is allowed to return to ambient temperature under stirring. After filtering and drying under vacuum, a white solid is obtained with a yield of 92%. Melting point: 185.3-186.0 °C.

<u>Example 2:</u> 2,6-di(tert-butyl)-4-(2-{[methyl(2-propynyl)amino]methyl}-1,3-thiazol-4-yl)phenol:

0.52 ml (3.7 mmol) of triethylamine and an excess of 0.56 g (7.5 mmol) of chloropropargyl are added dropwise at 0°C to a solution of 0.5 g (1.5 mmol) of the compound of Example 1 in 15 ml of acetonitrile. After stirring overnight, the reaction mixture is concentrated under vacuum and the residue is diluted with dichloromethane and 50 ml of a saturated solution of NaCl. After stirring and decantation, the organic

phase is separated and dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 20% ethyl acetate in heptane). After evaporation, the pure fractions produce a white solid with a yield of 20%. Melting point: 210-215 °C.
MH+ = 371.20.

Example 3: 2-[({4-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl}methyl)(methyl)amino]acetonitrile:

The experimental protocol used is identical to that described for Example 2, chloroacetonitrile being used as starting product in place of the chloropropargyl. A beige solid is obtained with a yield of 54%. Melting point: 150-156 °C.
MH+ = 372.30

Example 4: 5-[({4-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl}methyl)(methyl)amino]pentanenitrile:

The experimental protocol used is identical to that described for Example 2, bromovaleronitrile being used as starting product in place of the chloropropargyl. A yellow oil is obtained with a yield of 24%.
MH+ = 414.30

Example 5: 6-[({4-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl}methyl)(methyl)amino]hexanenitrile:

The experimental protocol used is identical to that described for Example 2, bromohexanenitrile being used as starting product in place of the chloropropargyl. A red oil is obtained with a yield of 35%.
MH+ = 428.40.

Example 6: 2,6-di(tert-butyl)-4-(2-{[(2-hydroxyethyl)(methyl)amino]methyl}-1,3-thiazol-4-yl)phenol:

The experimental protocol used is identical to that described for Example 2, 2-bromoethanol is used as starting product in place of the chloropropargyl. A yellow oil is obtained with a yield of 57%.
MH+ = 377.30

<u>Example 7:</u> 4-(2-{[benzyl(methyl)amino]methyl}-1,3-thiazol-4-yl)-2,6-di(tert-butyl)phenol:

The experimental protocol used is identical to that described for Example 2, benzyl chloride being used as starting product in place of the chloropropargyl. A white solid is obtained with a yield of 52%. Melting point: 165-170 °C.
MH+ = 423.30

<u>Example 8:</u> 2,6-di(tert-butyl)-4-{2-[(methyl-4-nitroanilino)methyl]-1,3-thiazol-4-yl}phenol:

This product is obtained according to the procedure described in the PCT Patent Application WO 98/58934.

<u>Example 9:</u> 2,6-di(tert-butyl)-4-(2-{[4-(dimethylamino)(methyl)anilino]methyl}-1,3-thiazol-4-yl)phenol:

0.8 ml of paraformaldehyde and 0.10 g of 10% palladium on carbon is added to a solution of 0.5 g (1.1 mmol) of Example 8 in 20 ml of ethanol. The medium is placed under hydrogen for 4 hours. The catalyst is filtered out and the solvent evaporated to dryness. The expected product is obtained after chromatography on a silica column (eluent: 3% ethanol in dichloromethane). The expected compound is obtained in the form of a brown oil with a yield of 54%.
MH+ = 452.30

<u>Example 10:</u> benzyl {4-[3,5-di(tert-butyl)-4-hydroxyphenyl]-1,3-thiazol-2-yl}methylcarbamate:

The compound is produced according to an experimental protocol described in the Patent Application WO 98/58934 (see preparation of intermediates 26.1 and 26.2), using Z-Gly-NH_2 in place of the N-Boc sarcosinamide. The expected compound is obtained in the form of a pale yellow oil with a yield of 99%.
MH+ = 453.20

<u>Example 11:</u> 4-[2-(aminomethyl)-1,3-thiazol-4-yl]-2,6-di(tert-butyl)phenol:

0.1 ml of a 40% solution of potassium hydroxide is added dropwise to a solution of 0.106 g (1.1 mmol) of the compound of Example 10 in 10 ml of methanol. After overnight stirring under reflux, the reaction mixture is concentrated under vacuum and the residue is diluted with dichloromethane and washed with a 1*N* solution of HCl then

with 50 ml of a saturated solution of NaCl. The organic phase is separated and dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 5% ethanol in dichloromethane) in the form of a brown foam with a yield of 76%.
MH+ = 319.29.

<u>Example 12:</u> 2,6-di(tert-butyl)-4-(2-{[methyl(4-nitrobenzyl)amino] methyl}-1,3-thiazol-4-yl)phenol:

The experimental protocol used is identical to that described for Example 2, 4-nitrobenzyl bromide being used as starting product in place of the chloropropargyl. A yellow solid is obtained with a yield of 63%. Melting point: 114.4-111.7 °C.
MH+ = 468.3

<u>Example 13:</u> 4-(2-{[(4-aminobenzyl)(methyl)amino]methyl}-1,3-thiazol-4-yl)-2,6-di(*tert*-butyl)phenol:

0.059 g (0.26 mmol) of $SnCl_2$. $2H_2O$ and 0.017 g (0.26 mmol) of Zn are added successively to a solution of 0.05 g (0.107 mmol) of the compound of Example 12 in a mixture of 0.55 ml of glacial acetic acid and 0.07 ml of a 12*N* solution of HCl. The mixture is stirred for 18 hours at 20 °C. The reaction mixture is then made basic by adding a 30% aqueous solution of NaOH. The product is then extracted using two times 50 ml of CH_2Cl_2. The organic solution is washed with 50 ml of salt water, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue is purified on a silica column (eluent: 5% ethanol in dichloromethane). A yellow gum is obtained with a yield of 52%.
MH+ = 438.29.

<u>Example 14:</u> 2,6-di(tert-butyl)-4-(2-{[(4-nitrobenzyl)amino]methyl}-1,3-thiazol-4-yl)phenol:

0.5 g (1.57 mmol) of the compound of Example 9, 0.237 g (1.57 mmol) of 4-nitrobenzaldehyde and 1 g of previously activated pulverulent 4 Å molecular sieve are added successively to a flask containing 30 ml of anhydrous MeOH, under an inert atmosphere. The reaction mixture is vigorously stirred for 18 hours before the addition, by portions, of 0.06 g (1.57 mmol) of $NaBH_4$. Stirring is maintained for another 4 hours before the addition of 5 ml of water. After a quarter of hour, the sieve is filtered out and the reaction mixture is extracted with two times 100 ml of CH_2Cl_2. The organic phase is washed successively with 50 ml of water then with 50 ml of salt water, dried over sodium sulphate, filtered and concentrated under vacuum. The residue is purified

on a silica column (eluent: 50% ethyl acetate in heptane). A yellow oil is obtained with a yield of 55%.
MH+ = 454.20.

Example 15: **4-(2-{[(4-aminobenzyl)amino]methyl}-1,3-thiazol-4-yl)-2,6-di(tert-butyl)phenol:**

The experimental protocol used is identical to that described for Example 13, the compound of Example 14 being used as starting product in place of the compound of Example 12. A yellow gum is obtained with a yield of 83%.
MH+ = 424.20.

The compounds of the examples 16 to 22 can be obtained according to the procedures described in the PCT Patent Application WO 98/58934.

Example 16: **4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-aminophenyl)-2-thiazolemethanamine:**

[is intermediate 26.5 of the PCT Application WO 98/58934]

Example 17: **4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-1H-imidazole-2-methanamine:**

Intermediate 26.2 of the PCT Application WO 98/58934 is subjected to a hydrogenation as described in Stage 1.2 of the same document using ethanol as reaction solvent in place of methanol. The expected product is isolated in the form of a red foam.
MH+ = 316.33.

Example 18: **4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrophenyl)-1H-imidazole-2-methanamine:**

[is intermediate 27.2 of the PCT Application WO 98/58934]

Example 19: **4-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-aminophenyl)-1H-imidazole-2-methanamine:**

[is intermediate 27.3 of the PCT Application WO 98/58934]

Example 20: **4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-nitrobenzoyl)-1H-imidazole-2-methanamine:**

[is intermediate 22.6 of the PCT Application WO 98/58934]

Example 21: **4-[3,5-bis-(1,1-dimethylethyl)-4-hydroxyphenyl]-N-methyl-N-(4-aminobenzoyl)-1H-imidazole-2-methanamine:**

[is intermediate 22.7 of the PCT Application WO 98/58934]

Example 22: **3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4,5-dihydro-5-isoxazoleethanol:**

[is intermediate 28.1 of the PCT Application WO 98/58934]

The compound of Example 23 can be obtained according to the procedures described in the PCT Patent Application WO 99/09829.

Example 23: **2-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-4-oxazoleethanol:**

[is intermediate 1.C of the PCT Application WO 99/09829; alternatively, this compound can also be obtained according to the procedure described in *J. Med. Chem.* (1996), **39**, 237-245.]

Example 24: **4-[{[4-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl}(methyl)amino]butanenitrile:**

The experimental protocol used is identical to that described for Example 2, bromobutyronitrile being used as starting product in place of the chloropropargyl. A yellow oil is obtained with a yield of 18%.
MH^+ = 400.30.

Example 25: **2,6-ditert-butyl-4-(2-{[(3-nitrobenzyl)amino]methyl}-1,3-thiazol-4-yl)phenol:**

The experimental protocol used is identical to that described for Example 14, 3-nitrobenzaldehyde being used as starting product in place of the 4-nitrobenzaldehyde. A yellow oil is obtained with a yield of 28%.
MH+ = 454.20.

Example 26: **2,6-ditert-butyl-4-(4-{2-[methyl(2-propynyl)amino]ethyl}-1,3-oxazol-2-yl)phenol:**

The compound of Example 23 is converted to brominated derivative, intermediate 3, according to the procedure indicated in Diagram 1(c) of the PCT Application WO 99/09829. Then the brominated derivative (0.5 g;1.31 mmol) is added to a solution of N-methylpropargylamine 0.34 ml (3.94 mmol) and potassium carbonate (1.11 g) in

dimethylformamide (20 ml). After overnight stirring at 80 °C, the reaction mixture is concentrated under vacuum and the residue is diluted with dichloromethane and 50 ml of a saturated solution of NaCl. After stirring and decantation, the organic phase is separated and dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 50% ethyl acetate in heptane). After evaporation, the pure fractions produce a yellow oil with a yield of 24%.
MH+ = 369.30.

<u>Example 27:</u> [{2-[2-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl}(methyl)amino]acetonitrile:

The experimental protocol used is identical to that described for the compound of Example 26, methylaminoacetonitrile being used as starting product in place of the N-methylpropargylamine. A white solid is obtained with a yield of 36%. Melting point: 165-167.8 °C.

<u>Example 28:</u> 3-[{2-[2-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl}(methyl)amino]propanenitrile:

The experimental protocol used is identical to that described for Example 26, N-methyl-β-alaninenitrile being used as starting product in place of the N-methylpropargylamine. A white solid is obtained with a yield of 56%. Melting point: 104-104.8 °C.

<u>Example 29:</u> 2,6-ditert-butyl-4-{4-[2-(1-piperazinyl)ethyl]-1,3-oxazol-2-yl}phenol hydrochloride:

29.1) *tert-butyl 4-{2-[2-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-oxazol-4-yl]ethyl}-1-piperazinecarboxylate*

The experimental protocol used is identical to that described for Example 26, *tert*-butyl piperazinecarboxylate being used as starting product in place of the N-methylpropargylamine. A brown oil is obtained with a yield of 72%.
MH+ = 486.20.

29.2) *2,6-ditert-butyl-4-{4-[2-(1-piperazinyl)ethyl]-1,3-oxazol-2-yl}phenol hydrochloride*

A stream of HCl gas is passed bubblewise into a solution at 0 °C of intermediate 29.1 (0.450 g; 9.27 mmol) in ethyl acetate (30 ml). The mixture is left to return to ambient temperature overnight. A stream of argon is passed through the reaction mass, then the

powder obtained is filtered and washed with ethyl acetate then with ether in order to produce a white solid with a yield of 70%. Melting point: > 200 °C.

__Example 30:__ **N-methyl[4-(10H-phenothiazin-2-yl)-1,3-thiazol-2-yl]methanamine hydrochloride:**

The experimental protocol used is identical to that described for Example 1, 2-bromo-1-(10H-phenothiazin-2-yl)ethanone (*J. Heterocyclic. Chem.*, (1978), **15**, 175-176 and *Arzneimittel Forschung*, (1962), **12**, 48), being used as starting product in place of the 2-bromo-1-(3,5-ditert-butyl-4-hydroxyphenyl)ethanone. The product obtained is purified by recrystallization from glacial acetic acid in order to produce a greenish solid. Melting point: > 275 °C.

Alternatively, this compound can be obtained according to a similar method, but using 2-chloro-1-(10H-phenothiazin-2-yl)ethanone instead of 2-bromo-1-(10H-phenothiazin-2-yl)ethanone:

30.1) 2-chloro-1-(10H-phenothiazin-2-yl)ethanone

2-bromo-1-[10-(chloroacetyl)-10*H*-phenothiazin-2-yl)ethanone (2.2 g; 5.55 mmol; prepared according to a protocol described in *J. Heterocyclic. Chem.* (1978), **15**, 175, followed by a Friedel-Crafts reaction) is dissolved hot in a mixture of acetic acid (20 ml) and 20% HCl (5.5 ml) and the mixture obtained is heated under reflux for 30 minutes. The reaction mixture is allowed to cool down, the precipitate is filtered, the mixture rinsed with acetic acid (5 ml) and dried under vacuum, the solid obtained is purified by crystallization from toluene in order to produce a brown product with a yield of 82%. Melting point: 190-191 °C (value in the literature: 197-198 °C).

30.2) N-methyl[4-(10H-phenothiazin-2-yl)-1,3-thiazol-2-yl]methanamine hydrochloride

Intermediate 30.1 (0.280 g; 1.0 mmol) and *tert*-butyl 2-amino-2-thioxoethyl(methyl)carbamate (0.204 g; 1.0 mmol; described for example in PCT Patent Application WO 98/58934) are dissolved in toluene and the mixture is heated under reflux for 18 hours. After the toluene is evaporated off and the reaction mixture cooled down to 0 °C, the latter is taken up in a 4*N* solution of HCl in dioxane (10 ml) and the mixture stirred for one hour at 0 °C before allowing the temperature to return to ambient temperature. The solid formed is filtered and rinsed with ether. The expected product is obtained after purification by crystallization from hot acetic acid in order to obtain a greenish solid. Melting point: >275 °C.

Example 31: butyl 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylcarbamate

31.1) N-(butoxycarbonyl)-β-alanine

A solution containing β-alanine (8.9 g; 0.1 mol) and 100 ml of a 1N solution of sodium hydroxide is cooled down to 10 °C. *n*-butyl chloroformate (13.66 g; 0.1 mol) and 50 ml of a 2N solution of sodium hydroxide are added simultaneously. After stirring for 16 hours at 23 °C, approximately 10 ml of a solution of concentrated hydrochloric acid (approximately 11 N) is added in order to adjust the pH to 4-5. The oil obtained is extracted with ethyl acetate (2 x 50 ml), washed with water then dried over magnesium sulphate. The product crystallizes from isopentane in the form of a white powder (yield of 68%). Melting point: 50.5 °C.

31.2) butyl 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylcarbamate

A mixture of N-(butoxycarbonyl)-β-alanine (prepared in Stage 31.1; 5.67 g; 0.03 mol) and caesium carbonate (4.89 g; 0.015 mol) in 100 ml of ethanol is stirred at 23°C for 1 hour. The ethanol is eliminated by evaporation under reduced pressure in a rotary evaporator. The mixture obtained is dissolved in 100 ml of dimethylformamide then 4-phenyl-bromoacetophenone (8.26 g; 0.03 mol) is added. After stirring for 16 hours, the solvent is evaporated off under reduced pressure. The mixture obtained is taken up in ethyl acetate then the caesium bromide is filtered. The ethyl acetate of the filtrate is evaporated and the reaction oil is taken up in a mixture of xylene (100 ml) and ammonium acetate (46.2 g; 0.6 mol). The reaction medium is heated at reflux for approximately one hour and 30 minutes then, after cooling down, a mixture of ice-cooled water and ethyl acetate is poured into the reaction medium. After decantation, the organic phase is washed with a saturated solution of sodium bicarbonate, dried over magnesium sulphate then evaporated under vacuum. The solid obtained is filtered then washed with ether in order to produce a light beige-coloured powder (yield of 50%). Melting point: 136.7°C.
MH+ = 364.3.

Example 32: N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl]pentanamide

32.1) tert-butyl 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylcarbamate

This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31, N-(tert-butoxycarbonyl)-β-alanine acid replacing the β-alanine. A yellow-coloured powder is obtained with a yield of 37%.

MH+ = 364.2.

32.2) 2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethylamine

tert-butyl 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylcarbamate (4.8 g; 0.013 mol) is stirred in 120 ml of a solution of ethyl acetate saturated in hydrochloric acid for 2 hours 30 minutes at a temperature of 55 °C. The solid obtained is filtered and washed with ether. A light beige-coloured powder is obtained with a yield of 89%.
MH+ = 264.2.

32.3) N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl]pentanamide

A mixture containing valeric acid (0.24 ml; 0.002 mol), dicyclohexylcarbodiimide (2.2 ml; 1M solution in methylene chloride) and 1-hydroxybenzotriazole hydrate (336 mg; 0.0022 mol) in 15 ml of dimethylformamide (DMF) is stirred at 23°C for thirty minutes. The 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylamine prepared previously is added then the mixture is stirred for 48 hours at 23 °C. The dicyclohexylurea formed is filtered then the DMF is evaporated off under reduced pressure. The residue obtained is taken up in ethyl acetate then the residual dicyclohexylurea is filtered again. The filtrate is washed with water and extracted using ethyl acetate. The solvent is evaporated off then purification is carried out on a silica column (eluent: CH_2Cl_2-MeOH / 95-05). A white-coloured powder is obtained with a yield of 13%. Melting point : 166-167 °C.
MH+ = 348.2.

<u>Example 33:</u> N-[2-(4-[1,1'-biphenyl]-4-yl-1H-imidazol-2-yl)ethyl]-1-butanesulphonamide

A mixture containing 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylamine (obtained in Stage 32.2 of Example 32; 660 mg; 0.0025 mol) and *n*-butane sulphochloride (390 mg; 0.0025 mol) in 20 ml of DMF is stirred for two hours at 23 °C. Potassium carbonate (345 mg; 0.0025 mol.) is then added, then stirring is continued for two hours. The solvent is evaporated off and the reaction mixture is taken up in water and dichloromethane. The organic phase is washed with a saturated solution of sodium chloride then dried. The solvent is evaporated off and the residue obtained is purified on a silica column (eluent: CH_2Cl_2-MeOH / 93-07). A light beige-coloured powder is obtained with a yield of 19%. Melting point: 168.5 °C.
MH+ = 384.2.

<u>Example 34</u>: 4-[2-(2-{[butylamino)carbonyl]amino}ethyl)-1H-imidazol-4-yl]-1,1'-biphenyl

A mixture containing 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylamine (obtained in Stage 32.2 of Example 32; 660 mg; 0.0025 mol) and *n*-butyl isocyanate (341 mg; 0.0025 mol) in 20 ml of 1,2-dichloroethane is stirred for fifteen minutes at 60 °C. The suspension is stirred for sixteen hours at 23 °C and filtered. The solid obtained is washed with 1,2-dichloroethane and with ether. A white-coloured powder is obtained with a yield of 66%. Melting point: 178°C.
MH+ = 363.3.

<u>Example 35:</u> N-{(S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl}cyclobutanamine

35.1 tert-butyl) (S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methylcarbamate

This compound is obtained according to an operating method similar to the preparation of the compound of Stage 31.2 of Example 31 using Boc-aminocyclohexylglycine (9.4 g; 0.036 mol) in place of the N-(butoxycarbonyl)-β-alanine and parafluorobromoacetophenone (7.9 g; 0.036 mol) in place of the 4-phenyl-bromoacetophenone. A white-coloured powder is obtained with a yield of 53%.
MH+ = 374.2.

35.2) (S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methanamine

This compound is prepared according to an operating method similar to that of Stage 32.2 of Example 32 using *tert*-butyl (S)-cyclohexyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methylcarbamate (7.5 g; 0.02 mol) as starting compound. A white-coloured powder is obtained with a yield of 92%.
MH+ = 274.2.

35.3) N-{(S)-cyclohexyl[4-(4-fluorophenyl)-1H-imidazol-2-yl]methyl}cyclobutanamine

A mixture containing (S)-cyclohexyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methanamine (prepared in Stage 5.2; 519 mg; 0.0015 mol), triethylamine (0.4 ml; 0.003 mol) and butanone (140 mg; 0.002 mol) in 10 ml of methanol is stirred for thirty minutes at 23 °C. Sodium triacetoxyborohydride (630 mg; 0.003 mol) is then added. The reaction mixture is stirred for sixteen hours then poured into water. After extraction with ethyl acetate, the organic phase is washed with a saturated solution of

sodium chloride then dried over magnesium sulphate. The solvent is evaporated off and the residue is purified on a silica column (eluent: CH_2Cl_2-MeOH mixture / 95-05). A white-coloured powder is obtained with a yield of 12%. Melting point : 170-172 °C. MH+ = 328.2.

Example 36: N-[1-(4-cyclohexyl-1H-imidazol-2-yl)heptyl]cyclohexanamine

36.1) 2-bromo-1-cyclohexylethanone

Cyclohexylacetone (5.4 ml, 0.039 mol) and bromine (2 ml, 0.039 mol) are stirred at 23 °C in 100 ml of methanol. After decolourization, 100 ml of water are gently added. The mixture obtained is neutralized with 5 g of sodium bicarbonate. Extraction is carried out with ether followed by washing the organic phase with 100 ml of water. After drying over magnesium sulphate, the mixture is concentrated with a rotary evaporator. An oil is obtained with a yield of 97%.
NMR ^1H (δ ppm, DMSO): 1.21-1.27 (m, 5H); 1.59-1.83 (m, 5H); 2.59-2.64 (m, 1*H*); 4.42 (s, 2H).

36.2) 2-[(tert-butoxycarbonyl)amino]octanoic acid

A mixture of 2-amino-octanoic acid (25.25 g; 0.156 mol) and di-*tert*-butyl dicarbonate (37.8 g; 0.173 mol) in 425 ml of dioxane is stirred at reflux for three hours. After returning to 23 °C, the mixture is again stirred for twenty four hours then the insoluble part is filtered out. The filtrate is evaporated. An oil is obtained with a yield of 99%.
NMR H^1 (δ ppm, DMSO): 0.85 (t, 3H); 1.11-1.27 (m, 8H); 1.37 (s, 9H); 1.51-1.65 (m, 2H); 3.81-3.87 (m, 1*H*); 6.96-6.97 (m, 1*H*); 12.3 (s, 1*H*).
IR (cm^{-1}): 3500; 2860; 1721 ($\nu_{C=O}$ (acid)); 1680 ($\nu_{C=O}$ (carbamate)); 1513 (ν_{C-NH} (carbamate)).

36.3) tert-butyl 1-(4-cyclohexyl-1H-imidazol-2-yl)heptylcarbamate

This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31, using 2-[(tert-butoxycarbonyl)amino]octanoic acid (8.1 g; 0.0314 mol) in place of the N-(butoxycarbonyl)-β-alanine and 2-bromo-1-cyclohexylethanone (6.4 g; 0.0314 mol) in place of the 4-phenyl-bromoacetophenone. An oil is obtained which is sufficiently pure to be used in the following reaction (yield of 88%).

36.4) 1-(4-cyclohexyl-1H-imidazol-2-yl)-1-heptanamine

This compound is obtained according to an operating method similar to that of Stage 32.2 of Example 32 using as starting compound *tert*-butyl 1-(4-cyclohexyl-1*H*-

imidazol-2-yl)heptylcarbamate (prepared in Stage 6.3; 10 g; 0.0275 mol). A yellow solid is obtained in the form of a paste (yield of 37%).
MH+ = 264.2.

36.5) N-[1-(4-cyclohexyl-1H-imidazol-2-yl)heptyl]cyclohexanamine

This compound is obtained according to an operating method similar to that of Stage 35.3 of Example 35 using as starting amine 1-(4-cyclohexyl-1*H*-imidazol-2-yl)-1-heptanamine (obtained in Stage 6.4; 2.5 g; 0.074 mol) and as ketone, cyclohexanone (1 ml; 0.0097 mol). After purification on a silica column (eluent: ethyl acetate - heptane / 7-3 with CH_2Cl_2-MeOH / 95-05), a white-coloured powder is obtained with a yield of 12%. Melting point : 172-174 °C.
MH+ = 346.3.

Example 37: N-{1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexyl}-N-cyclohexylamine

37.1) 2-[(tert-butoxycarbonyl)amino]-6-methylheptanoic acid

A solution of diisopropylamine (13.2 ml; 0.094 mol) in 130 ml of tetrahydrofuran (THF) is cooled down to -40 °C. *n*-butyllithium (37 ml of a 2.5 M solution in hexane; 0.094 mol) is added dropwise. The temperature is allowed to rise to 0 °C. At this temperature, Boc-glycine (5 g; 0.028 mol) in solution in 30 ml of THF is introduced into the mixture. The reaction medium is left for ten minutes at this temperature then 1-bromo-4-methylpentane (7.9 ml; 0.056 mol) in solution in 20 ml of THF is added rapidly. The temperature is allowed to return to 23 °C and the mixture is stirred at this temperature for one hour. After hydrolysis with 100 ml of water then acidification with 150 ml of a saturated solution of potassium hydrogen sulphate, the mixture obtained is extracted twice with 50 ml of ethyl acetate. The organic phase is washed with 100 ml of water then with 100 ml of a saturated solution of sodium chloride. After drying over magnesium sulphate and evaporating the solvent, the residue obtained is purified on a silica column (eluent: ethyl acetate - heptane / 6-4) in order to produce a white-coloured powder with a yield of 50%.
MH+ = 260.3.

37.2) tert-butyl 1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexylcarbamate

This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31 using 2-[(tert-butoxycarbonyl)amino]-6-methylheptanoic acid (3.5 g; 0.0135 mol) in place of the N-(butoxycarbonyl)-β-alanine and 3-bromophenacyl

bromide (3.75 g; 0.0135 mol) in place of the 4-phenyl-bromoacetophenone. A white powder is obtained with a yield of 63%. Melting point: 134-136 °C.
MH+ = 436.2.

37.3) 1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methyl-1-hexanamine

This compound is obtained according to an operating method similar to that of Stage 32.2 of Example 32 using as starting compound *tert*-butyl 1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-5-methylhexylcarbamate (obtained in Stage 37.2; 3.5 g; 0.008 mol). A white-coloured powder is obtained with a yield of 97%. Melting point : 200-202 °C.
MH+ = 336.2.

37.4) N-{1-[4-(3-bromophenyl)-1H-imidazol-2-yl]-5-methylhexyl}- N-cyclohexylamine

This compound is obtained according to an operating method similar to that of Stage 35.3 of Example 35 using as starting amine, 1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-5-methyl-1-hexanamine (obtained in Stage 7.3; 0.8 g; 0.0019 mol) and as ketone, cyclohexanone (0.32 ml; 0.0023 mol). A white-coloured powder is obtained with a yield of 38%. Melting point: 236-238 °C.
MH+ = 418.2.

<u>Example 38:</u> N-{1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptyl}cyclohexanamine

38.1) tert-butyl 1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptylcarbamate

This compound is obtained according to an operating method similar to that of Stage 31.2 of Example 31 using 2-[(tert-butoxycarbonyl)amino]octanoic acid (6.2 g; 0.024 mol) in place of the N-(butoxycarbonyl)-β-alanine and 2-bromo-4-fluoroacetophenone (5.2 g; 0.024 mol) in place of the 4-phenyl-bromoacetophenone. A white powder is obtained (yield: 58%) which is sufficiently pure to be used as it is for the following stage.

38.2) 1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-1-heptanamine

This compound is obtained according to an operating method similar to that of Stage 32.2 of Example 32 using as starting compound *tert*-butyl 1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]heptylcarbamate (5.2 g; 0.014 mol). After purification on a silica column (eluent: CH_2Cl_2-MeOH-NH_4OH / 89-10-1), a grey-coloured powder is obtained (yield of 72%). Melting point : 148-150 °C.
MH+ = 276.2.

38.3) N-{1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]heptyl}cyclohexanamine

This compound is obtained according to an operating method similar to that of Stage 35.3 of Example 35 using as starting amine, 1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine (0.5 g; 0.0014 mol) and as ketone, cyclohexanone (0.17 ml; 0.0014 mol). A white-coloured powder is obtained with a yield of 15%.

Melting point: 190-192°C.
MH+ = 358.2.

<u>Example 39:</u> (1*R*)-*N*-benzyl-1-(1-benzyl-4-*tert*-butyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)ethanamine

Triethylamine (0.83 ml; 0.006 mol) is added at 23 °C to a solution containing (1*R*)-1-(1-benzyl-4-*tert*-butyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)ethanamine (0.7 g; 0.002 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) in 15 ml of acetonitrile. The mixture is stirred for one hour at 23°C then benzyl chloride (0.23 ml; 0.002 mol) is added. Stirring is maintained for 16 hours. The reaction mixture is concentrated using a rotary evaporator and the oil obtained is taken up in ethyl acetate and water. The aqueous phase is extracted with ethyl acetate and washed with water then with a saturated solution of sodium chloride. The solvents are evaporated off under vacuum. After purification on a silica column (eluent: AE-heptane / 7-3), a deep beige-coloured solid is obtained in the form of a paste (yield of 5%). Free base. Melting point: 60-62 °C.
MH+ = 463.3.

<u>Example 40:</u> (R,S)-*N*-benzyl-1-(1-benzyl-4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine

(R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)heptylamine (1 g; 0.003 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 20 ml of dimethylformamide. Potassium carbonate (2.2 g; 0.016 mol) is added at 23 °C then benzyl bromide (1.2 ml; 0.010 mol) is added fairly slowly. The mixture is stirred for 72 hours at 23 °C before being poured into ice-cooled water. The mixture is extracted with ethyl acetate. The organic phase is washed with water then with a saturated solution of sodium chloride. After drying over magnesium sulphate, the solvents are concentrated using a rotary evaporator. After purification on a silica column (eluent: ethyl acetate-heptane / 10-90), a white-coloured powder is obtained (yield of 31%). Free base. Melting point: 94-96 °C.
MH+ = 438.3.

<u>Example 41:</u> *N*-benzyl-*N*-[(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methyl]-1-hexanamine

N-benzyl(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methanamine (1 g; 0.0024 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 15 ml of dimethylformamide. Potassium carbonate (1 g; 0.0073 mol) is added at 23 °C then hexane bromide (0.34 ml; 0.0024 mol) is added fairly slowly. The reaction mixture is brought to about 70°C for 3 hours before being poured into ice-cooled water. The mixture is extracted with ethyl acetate and the organic phase is washed with water. After drying over magnesium sulphate, the solvents are concentrated using a rotary evaporator. After purification on a silica column (eluent: ethyl acetate-heptane / 7-3), a light yellow-coloured solid is obtained in the form of a paste (yield of 13%). Free base. Melting point: 120-122 °C. MH+ = 424.3.

<u>Example 42:</u> *N*-benzyl(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-*N*-methylmethanamine

(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-*N*-methylmethanamine (1 g; 0.003 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 20 ml of dimethylformamide. Potassium carbonate (1.23 g; 0.009 mol) is added at 23 °C then benzyl bromide (0.34 ml; 0.003 mol) is added fairly slowly. The reaction mixture is stirred at this temperature for 48 hours then poured in ice-cooled water. The mixture is extracted with ethyl acetate and the organic phase washed with water. After drying over magnesium sulphate, the solvents are concentrated using a rotary evaporator. After purification on a silica column (eluent: ethyl acetate-heptane / 8-2), a white-coloured solid is obtained in the form of a paste (yield of 16%). Free base. Melting point: 106-108 °C. MH+ = 354.2.

<u>Example 43:</u> (R,S)-*N*,*N*-dihexyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine

(R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine (1 g; 0.003 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 10 ml of methanol. Triethylamine (0.9 ml; 0.006 mol) is added dropwise then the mixture is stirred for 30 minutes at 23 °C. Hexanal (0.45 ml; 0.0036 mol) is then added then the mixture is stirred for one hour at 23°C. Sodium triacetoxyborohydride (1.3 g; 0.006 mol) is finally added. After stirring for two hours at 23 °C, water is added and the reaction mixture is extracted with ethyl acetate.

The organic phase is washed with water and dried over magnesium sulphate before evaporation of the solvents. After purification on a silica column (eluent: ethyl acetate-heptane / 6-4), a brown-coloured solid is obtained in the form of a paste (yield of 3%). Free base. The melting point could not be measured (paste).
MH+ = 426.4.

<u>Example 44:</u> ***N*-[(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]-2-pyrimidinamine**

(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine (2 g; 0.0066 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 10 ml of *n*-butanol. 2-bromopyrimidine (1 g; 0.0066 mol) then diisoethylamine (1.15 ml, 0.0066 mol) are added dropwise. The mixture is then heated to about 80 °C for 16 hours. The *n*-butanol is evaporated off then the residue is taken up in water and ethyl acetate. The organic phase is washed with water then with a saturated solution of sodium chloride before being dried over magnesium sulphate and concentrated using a rotary evaporator. After purification on a silica column (eluent: ethyl acetate-heptane / 7-3 then CH_2Cl_2-MeOH-NH_4OH/ 95-4.5-0.5 then ethyl acetate), a white-coloured powder is obtained (the yield is 20%). Free base. Melting point: 138-140 °C.
MH+ = 381.2.

<u>Example 45:</u> **(1-benzyl-4-phenyl-1*H*-imidazol-2-yl)-*N*,*N*-dimethylmethanamine**

(1-benzyl-4-phenyl-1*H*-imidazol-2-yl)methanamine (0.6 g; 0.0018 mol; prepared under experimental conditions similar to those previously and using suitable starting reagents and reaction products) is diluted in 15 ml of tetrahydrofuran. Triethylamine (1.12 ml; 0.008 mol) then methyl 4-toluenesulphonate (0.75 g; 0.004 mol) are added dropwise. The mixture is stirred for 48 hours at 23°C then poured into ice-cooled water. After extraction with ether then decantation, the organic phase is washed with water then with a saturated solution of sodium chloride. The organic phase is then dried over magnesium sulphate and concentrated using a rotary evaporator. After purification on a silica column (eluent: ethyl acetate-heptane / 7-3 then CH_2Cl_2-MeOH / 95-5), a white-coloured powder is obtained (yield of 44%). Free base. Melting point: 78-80 °C.
MH+ = 292.2.

Example 46: **(1*R*)-*N*-benzyl-2-(1*H*-indol-3-yl)-*N*-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

(1*R*)-*N*-benzyl-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine (0.5 g; 0.00127 mol; prepared under experimental conditions similar to that of Example 38 and using suitable starting reagents and reaction products) is diluted in 25 ml of tetrahydrofuran. Methyl tosylate (0.24 g; 0.00127 mol) is added to the previous solution at 23 °C then potassium *tert*-butylate (0.15 g; 0.00127 mol) is added fairly slowly. Stirring is maintained for two hours at 23°C then the mixture is heated to about 60°C for eight hours. The solvent is evaporated off and the residue obtained taken up in ethyl acetate and a 10% solution of sodium bicarbonate. After decantation, the organic phase is washed with water and dried over magnesium sulphate. The solvent is then evaporated off. After purification on a silica column (eluent: ethyl acetate-heptane / 7-3), a light beige-coloured solid is obtained in the form of a paste (yield of 4%). Free base. Melting point: 110-112 °C.
MH+ = 407.3.

The compounds of Examples 47 to 318 are obtained, according to procedures similar to those described for Examples 31 to 46 or above in the part entitled "Preparation of the compounds of general formula (I)".

Example 47: **(1*R*)-2-(1*H*-indol-3-yl)-*N*-(2-phenylethyl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. The melting point could not be measured (paste).

Example 48: **(1*R*)-*N*-benzyl-2-phenyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. Melting point: 228-230 °C.

Example 49: ***N*-benzyl(4-phenyl-1*H*-imidazol-2-yl)methanamine**

Free base. The melting point could not be measured (paste).

Example 50: ***tert*-butyl (1*R*)-1-(4-*tert*-butyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)-ethylcarbamate**

Free base. Melting point: 104-106 °C.

<u>Example 51:</u> (4-phenyl-1*H*-imidazol-2-yl)methanamine

Hydrochloride. Melting point: 228-230 °C.

<u>Example 52:</u> 1-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethylamine

Hydrochloride. Melting point: 200-204 °C.

<u>Example 53:</u> *N*-[(1*S*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]-1-hexanamine

Hydrochloride. Melting point: 132-134 °C.

<u>Example 54:</u> *tert*-butyl (R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)heptylcarbamate

Free base. Melting point: 102-104 °C.

<u>Example 55:</u> (4-[1,1'-biphenyl]-4-yl-1-methyl-1*H*-imidazol-2-yl)methanamine

Hydrochloride. Melting point: 279-280 °C.

<u>Example 56:</u> (1*S*)-3-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-butanamine

Hydrochloride. Melting point: 150-152 °C.

<u>Example 57:</u> butyl 2-[4-(4-phenoxyphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. The melting point could not be measured (paste).

<u>Example 58:</u> (R,S)-*N*-[2-(1-methyl-1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]-1-butanamine

Free base. The melting point could not be measured (paste).

<u>Example 59:</u> (R,S)-4-(2-{1-[(*tert*-butoxycarbonyl)amino]pentyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 172-176 °C.

<u>Example 60:</u> (R,S)-*N*-benzyl-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-pentanamine

Free base. Melting point: 201-203 °C.

<u>Example 61:</u> ***N*-[2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethyl]-3,3-dimethyl-butanamide**

Free base. Melting point: 186-188 °C.

<u>Example 62:</u> **(1*R*)-*N*-benzyl-1-(4,5-dimethyl-1,3-oxazol-2-yl)-2-(1*H*-indol-3-yl)ethanamine**

Free base. The melting point could not be measured (paste).

<u>Example 63:</u> ***tert*-butyl (R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)hexylcarbamate**

Free base. The melting point could not be measured (paste).

<u>Example 64:</u> **(R,S)-*N*-hexyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. Melting point: 140-142 °C.

<u>Example 65:</u> **(R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)hexylamine**

Hydrochloride. Melting point: 146-148 °C.

<u>Example 66:</u> **(R,S)-*N*-benzyl-1-[4-(4-methoxyphenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Hydrochloride. Melting point: from 115 °C.

<u>Example 67:</u> **(R,S)-*N*-(2,6-dichlorobenzyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. The melting point could not be measured (paste).

<u>Example 68:</u> **(R,S)-*N*-(4-chlorobenzyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. The melting point could not be measured (paste).

<u>Example 69:</u> **(R,S)-1-[4-(3-methoxyphenyl)-1*H*-imidazol-2-yl]heptylamine**

Hydrochloride. Melting point: 110-112 °C.

Example 70: **(R,S)-*N*-(2-chlorobenzyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. The melting point could not be measured (paste).

Example 71: **(R,S)-*N*-(2-fluorobenzyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. The melting point could not be measured (paste).

Example 72: **(R,S)-*N*-butyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. The melting point could not be measured (paste).

Example 73: **(R,S)-*N*-isopentyl-*N*-[1-(4-phenyl-1*H*-imidazol-2-yl)heptyl]amine**

Free base. The melting point could not be measured (paste).

Example 74: **(R,S)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-*N*-hexyl-1-heptanamine**

Free base. The melting point could not be measured (paste).

Example 75: **(R,S)-*N*-pentyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. Melting point: 118-120 °C.

Example 76: **(R,S)-*N*-[1-(4-phenyl-1*H*-imidazol-2-yl)heptyl]cyclohexanamine**

Free base. Melting point: 68-70 °C.

Example 77: **(R,S)-*N*-benzyl-1-[4-(3,4-dichlorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Free base. Melting point: 192-194 °C.

Example 78: **butyl (4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methylcarbamate**

Free base. Melting point: 130-132 °C.

Example 79: **(R,S)-*N*-[1-(4-phenyl-1*H*-imidazol-2-yl)heptyl]cyclopentanamine**

Free base. The melting point could not be measured (paste).

<u>Example 80:</u> (*S*)-cyclohexyl(4-phenyl-1*H*-imidazol-2-yl)methylamine

Hydrochloride. Melting point: 208-210 °C.

<u>Example 81:</u> (R,S)-*N*-{1-[4-(2-chlorophenyl)-1*H*-imidazol-2-yl]heptyl}-cyclohexanamine

Hydrochloride. Melting point: 155-157 °C.

<u>Example 82:</u> *N*-[(*S*)-cyclohexyl(4-cyclohexyl-1*H*-imidazol-2-yl)methyl]-cyclohexanamine

Hydrochloride. Melting point: 180-182 °C.

<u>Example 83:</u> *N*-[(*S*)-cyclohexyl(4-phenyl-1*H*-imidazol-2-yl)methyl]-cyclobutanamine

Hydrochloride. Melting point: 210-212 °C.

<u>Example 84:</u> (R,S)-*N*-{1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]heptyl}-cyclobutanamine

Hydrochloride. Melting point: 144-146 °C.

<u>Example 85:</u> *N*-{(*S*)-cyclohexyl[4-(3-fluoro-4-methoxyphenyl)-1*H*-imidazol-2-yl]methyl}cyclobutanamine

Free base. Melting point: from 95 °C.

<u>Example 86:</u> *N*-((*S*)-cyclohexyl{4-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}methyl)cyclobutanamine

Free base. Foam.

<u>Example 87:</u> *N*-{(*S*)-cyclohexyl[4-(3-fluorophenyl)-1*H*-imidazol-2-yl]methyl}-cyclobutanamine

Free base. Melting point: 172-176 °C.

<u>Example 88:</u> (1*R*)-*N*-benzyl-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine

Free base. Melting point: 100-102 °C.

<u>Example 89:</u> (R,S)-2-(1*H*-indol-3-yl)-1-(5-methyl-4-phenyl-1*H*-imidazol-2-yl)ethanamine

Hydrochloride. Melting point: 208-210 °C.

<u>Example 90:</u> (1*R*)-1-(4,5-diphenyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)ethanamine

Hydrochloride. Melting point: > 260 °C.

<u>Example 91:</u> (R,S)-2-phenyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine

Hydrochloride. Melting point: 180-182 °C.

<u>Example 92:</u> (R,S)-2-(1-methyl-1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethylamine

Hydrochloride. Melting point: 110-114 °C.

<u>Example 93:</u> (1*S*)-*N*-benzyl-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine

Free base. Melting point: 118-120 °C.

<u>Example 94:</u> (1*R*)-*N*-benzyl-1-(4,5-diphenyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)ethanamine

Free base. Melting point: 146-148 °C.

<u>Example 95:</u> (1*R*)-*N*-benzyl-2-(1*H*-indol-3-yl)-1-(5-methyl-4-phenyl-1*H*-imidazol-2-yl)ethanamine

Free base. Melting point: 120-122 °C.

<u>Example 96:</u> *tert*-butyl (1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)-ethylcarbamate

Free base. Melting point: 208-210 °C.

<u>Example 97:</u> (1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine

Hydrochloride. The melting point could not be measured (paste).

<u>Example 98:</u> ***N*-[(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]benzamide**

Free base. Melting point: 218-220 °C.

<u>Example 99:</u> **benzyl (1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 105-108 °C.

<u>Example 100:</u> **(1*R*)-*N*-benzyl-2-(1*H*-indol-3-yl)-1-(4-phenyl-1,3-thiazol-2-yl)ethanamine**

Free base. Melting point: 134-136 °C.

<u>Example 101:</u> ***N*-[(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1,3-thiazol-2-yl)-ethyl]benzamide**

Free base. Melting point: 108-110 °C.

<u>Example 102:</u> ***tert*-butyl (1*R*)-2-(1*H*-indol-3-yl)-1-[4-(4-nitrophenyl)-1*H*-imidazol-2-yl]-ethylcarbamate**

Free base. Melting point: 220-222 °C.

<u>Example 103:</u> ***tert*-butyl (4-phenyl-1*H*-imidazol-2-yl)methylcarbamate**

Free base. Melting point: 170-172 °C.

<u>Example 104:</u> ***tert*-butyl (1-benzyl-4-phenyl-1*H*-imidazol-2-yl)methylcarbamate**

Free base. Melting point: 140-142 °C.

<u>Example 105:</u> **(R,S)-*N*-benzyl-2-(6-fluoro-1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. Melting point: 98-100 °C.

<u>Example 106:</u> **(1*R*)-2-(1*H*-indol-3-yl)-1-[4-(4-nitrophenyl)-1*H*-imidazol-2-yl]ethanamine**

Hydrochloride. Melting point: becomes pasty at about 220 °C.

<u>Example 107:</u> **(1-benzyl-4-phenyl-1*H*-imidazol-2-yl)methanamine**

Hydrochloride. Melting point: 248-250 °C.

<u>Example 108:</u> **(1*R*)-2-(1*H*-indol-3-yl)-*N*-(2-phenoxyethyl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. Melting point: 94-96 °C.

<u>Example 109:</u> **(1*R*)-1-(4-*tert*-butyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)ethylamine**

Hydrochloride. Melting point: 230-232 °C.

<u>Example 110:</u> ***N*-benzyl(1-benzyl-4-phenyl-1*H*-imidazol-2-yl)methanamine**

Free base. Melting point: 60-62 °C.

<u>Example 111:</u> **(1*R*)-2-(1-benzothien-3-yl)-*N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. Melting point: 152-154 °C.

<u>Example 112:</u> **(1*R*)-2-(1*H*-indol-3-yl)-*N*-(2-phenoxyethyl)-1-(4-phenyl-1,3-thiazol-2-yl)ethanamine**

Free base. Melting point: 124-126 °C.

<u>Example 113:</u> ***tert*-butyl 1-(4-phenyl-1*H*-imidazol-2-yl)cyclohexylcarbamate**

Free base. Melting point: 170-172 °C.

<u>Example 114:</u> ***tert*-butyl (R,S)-2-(6-chloro-1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 208-210 °C.

<u>Example 115:</u> **1-(4-phenyl-1*H*-imidazol-2-yl)cyclohexanamine**

Hydrochloride. Melting point: 202-204 °C.

<u>Example 116:</u> ***N*-[(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]-*N*'-phenylurea**

Free base. Compound described in the PCT Application WO 99/64401.

Example 117: ***N*-[(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]benzenecarboximidamide**

Free base. Compound described in the PCT Application WO 99/64401.

Example 118: **(1*R*)-*N*-(cyclohexylmethyl)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. Compound described in the PCT Application WO 99/64401.

Example 119: **(R,S)-*N*[1]-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1,5-pentanediamine**

Free base. Compound described in the PCT Application WO 99/64401.

Example 120: ***tert*-butyl (R,S)-5-(benzylamino)-5-(4-phenyl-1*H*-imidazol-2-yl)pentylcarbamate**

Free base. Compound described in the PCT Application WO 99/64401.

Example 121: ***N*-[(1*R*)-2-(1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethyl]-4-methoxybenzenecarboximidamide**

Free base. Compound described in the PCT Application WO 99/64401.

Example 122: **(R,S)-2-(6-chloro-1*H*-indol-3-yl)-1-(4-phenyl-1*H*-imidazol-2-yl)ethylamine**

Hydrochloride. Melting point: 210-212 °C.

Example 123: ***N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)cyclohexanamine**

Free base. Melting point: 114-116 °C.

Example 124: ***tert*-butyl (1*R*)-3-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)butylcarbamate**

Free base. Melting point: 88-90 °C.

Example 125: **(1*R*)-*N*-benzyl-3-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-butanamine**

Free base. Melting point: 134-135 °C.

Example 126: ***tert*-butyl (R,S)-phenyl(4-phenyl-1*H*-imidazol-2-yl)methylcarbamate**

Free base. Melting point: 134-136 °C.

Example 127: ***tert*-butyl 1-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 130-132 °C.

Example 128: **(R,S)-phenyl(4-phenyl-1*H*-imidazol-2-yl)methylamine**

Hydrochloride. The melting point could not be measured (paste).

Example 129: ***tert*-butyl (1*R*)-3-phenyl-1-(4-phenyl-1*H*-imidazol-2-yl)propylcarbamate**

Free base. Melting point: 72-74 °C.

Example 130: ***tert*-butyl (1*R*)-2-cyclohexyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 184-185 °C.

Example 131: **(1*R*)-3-phenyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-propanamine**

Hydrochloride. Melting point: 174-176 °C.

Example 132: **(1*R*)-2-cyclohexyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Hydrochloride. Melting point: 196-198 °C.

Example 133: **(R,S)-*N*-benzyl(phenyl)(4-phenyl-1*H*-imidazol-2-yl)methanamine**

Free base. Melting point: 144-146 °C.

Example 134: **(1*R*)-*N*-benzyl-2-cyclohexyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. Melting point: 52-54 °C.

Example 135: **(1*R*)-*N*-benzyl-3-phenyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-propanamine**

Free base. Melting point: 142-144 °C.

Example 136: **(R,S)-*N*-{5,5,5-trifluoro-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]pentyl}cyclohexanamine**

Free base. Melting point: 220 °C.

Example 137: **4-(2-{[(*tert*-butoxycarbonyl)amino]methyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 100-102 °C.

Example 138: ***N*-{(*S*)-cyclohexyl[4-(4-methylsulphonylphenyl)-1*H*-imidazol-2-yl]methyl}cyclohexanamine**

Free base. Melting point: 152-154 °C.

Example 139: ***N*-benzyl-2-(4-phenyl-1*H*-imidazol-2-yl)-2-propanamine**

Free base. Melting point: 136-138 °C.

Example 140: **4-(1-benzyl-2-{[(*tert*-butoxycarbonyl)amino]methyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 167-169 °C.

Example 141: **(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methanamine**

Hydrochloride. Melting point: 240-242 °C.

Example 142: **(R,S) 1-(4-phenyl-1*H*-imidazol-2-yl)heptylamine**

Hydrochloride. Melting point: 131-134 °C.

Example 143: **(1-benzyl-4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methanamine**

Hydrochloride. Melting point: 170-174 °C.

Example 144: ***N,N*-dibenzyl(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methanamine**

Free base. Melting point: 70-74 °C.

Example 145: **(R,S)-*N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. Melting point: 160-162 °C.

<u>Example 146:</u> 4-(2-{[(*tert*-butoxycarbonyl)amino]methyl}-1-methyl-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 208-210 °C.

<u>Example 147:</u> *tert*-butyl (1*S*)-1-(4,5-diphenyl-1*H*-imidazol-2-yl)-2-(1*H*-indol-3-yl)ethylcarbamate

Free base. Melting point: 142-143 °C.

<u>Example 148:</u> *tert*-butyl (1*R*)-2-(1*H*-indol-3-yl)-1-(1-methyl-4-phenyl-1*H*-imidazol-2-yl)ethylcarbamate

Free base. Melting point: 96-100 °C.

<u>Example 149:</u> 4-(2-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 72-74 °C.

<u>Example 150:</u> 4-(2-{(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-2-cyclohexylethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 112-114 °C.

<u>Example 151:</u> (1*R*)-2-(1*H*-indol-3-yl)-1-(1-methyl-4-phenyl-1*H*-imidazol-2-yl)ethanamine

Hydrochloride. Melting point: 206-210 °C.

<u>Example 152:</u> 4-(2-{2-[(*tert*-butoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 140-142 °C.

<u>Example 153:</u> *tert*-butyl methyl[(5-methyl-4-phenyl-1*H*-imidazol-2-yl)methyl]carbamate

Free base. Melting point: 70-72 °C.

<u>Example 154:</u> (1*R*)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-2-cyclohexylethanamine

Hydrochloride. Melting point: 178-180 °C.

<u>Example 155:</u> (4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-*N*-methylmethanamine

Hydrochloride. Melting point: 218-220 °C.

<u>Example 156:</u> *tert*-butyl (4,5-diphenyl-1*H*-imidazol-2-yl)methyl(methyl)carbamate

Free base. Melting point: 170-172 °C.

<u>Example 157:</u> *tert*-butyl (4,5-diphenyl-1*H*-imidazol-2-yl)methylcarbamate

Free base. Melting point: 144-146 °C.

<u>Example 158:</u> *N*-methyl-(5-methyl-4-phenyl-1*H*-imidazol-2-yl)methanamine

Hydrochloride. Melting point: 218-220 °C.

<u>Example 159:</u> (R,S)-*N*,*N*-dibenzyl-1-(1-benzyl-4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine

Hydrochloride. Melting point: 130-132 °C.

<u>Example 160:</u> (4,5-diphenyl-1*H*-imidazol-2-yl)methanamine

Hydrochloride. Melting point: 210-212 °C.

<u>Example 161:</u> 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethanamine

Hydrochloride. Melting point: 228-230 °C.

<u>Example 162:</u> (4,5-diphenyl-1*H*-imidazol-2-yl)-*N*-methylmethanamine

Hydrochloride. Melting point: 198-200 °C.

<u>Example 163:</u> *N*-benzyl(4,5-diphenyl-1*H*-imidazol-2-yl)methanamine

Free base. Melting point: 160-162 °C.

Example 164: ***N*-benzyl-2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethanamine**

Free base. Melting point: 174-176 °C.

Example 165: **4-(2-{[benzyl(*tert*-butoxycarbonyl)amino]methyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 130-132 °C.

Example 166: **(1*R*)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-3-phenyl-1-propanamine**

Hydrochloride. Melting point: 215-218 °C.

Example 167: **4-(2-{(1*R*)-1-[(*tert*-butoxycarbonyl)amino]-3-phenylpropyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 154-156 °C.

Example 168: ***N*-benzyl(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)methanamine**

Hydrochloride. Melting point: > 250 °C.

Example 169: **(1*R*)-*N*-benzyl-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-2-cyclohexylethanamine**

Free base. Melting point: 233-238 °C.

Example 170: **(1*R*)-*N*-benzyl-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-3-phenyl-1-propanamine**

Free base. Melting point: 210-213 °C.

Example 171: **4-(2-{3-[(*tert*-butoxycarbonyl)amino]propyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 145-146 °C.

Example 172: **4-[2-(2-{[(*tert*-butylamino)carbothioyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl**

Free base. Melting point: 98-99 °C.

Example 173: ***tert*-butyl 6-(4-phenyl-1*H*-imidazol-2-yl)hexylcarbamate**

Free base. The melting point could not be measured (paste).

Example 174: ***tert*-butyl (R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)pentylcarbamate**

Free base. Melting point: 126 °C.

Example 175: **(R,S)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-pentanamine**

Hydrochloride. Melting point: 197-200 °C.

Example 176: ***N*-[2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethyl]-1-hexanamine**

Free base. Melting point: 152-154 °C.

Example 177: **4-[2-(2-{[(*tert*-butylamino)carbonyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl**

Free base. Melting point: 195-196 °C.

Example 178: ***N*-benzyl-3-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-propanamine**

Free base. Melting point: 254-256 °C.

Example 179: **3-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-propanamine**

Hydrochloride. Melting point: > 260 °C.

Example 180: **6-(4-phenyl-1*H*-imidazol-2-yl)hexylamine**

Hydrochloride. Melting point: 244-246 °C.

Example 181: **(R,S)-1-(4-phenyl-1*H*-imidazol-2-yl)pentylamine**

Hydrochloride. Melting point: 178-180 °C.

Example 182: ***tert*-butyl (R,S)-1-[4-(4-methylphenyl)-1*H*-imidazol-2-yl]heptylcarbamate**

Free base. Melting point: 77-80 °C.

Example 183: ***tert*-butyl (R,S)-1-[4-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptylcarbamate**

Free base. Melting point: 64-65 °C.

Example 184: **(R,S)-1-[4-(4-methylphenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Hydrochloride. Melting point: 157-160 °C.

Example 185: **(R,S)-1-[4-(2-methoxyphenyl)-1*H*-imidazol-2-yl]heptylamine**

Hydrochloride. Melting point: 238-240 °C.

Example 186: **(R,S)-*N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-pentanamine**

Free base. Melting point: 200-202 °C.

Example 187: ***tert*-butyl (R,S)-1-[4-(4-methoxyphenyl)-1*H*-imidazol-2-yl]heptylcarbamate**

Free base. Melting point: 125-127 °C.

Example 188: **(R,S)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-heptanamine**

Hydrochloride. Melting point: 182-184 °C.

Example 189: ***tert*-butyl (R,S)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]heptylcarbamate**

Free base. Melting point: 141-143 °C.

Example 190: **(R,S)-1-[4-(4-methoxyphenyl)-1*H*-imidazol-2-yl]heptylamine**

Hydrochloride. Melting point: 231-232 °C.

Example 191: **(R,S)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Hydrochloride. Melting point: 230-231 °C.

Example 192: **(R,S)-4-(2-{1-[(*tert*-butoxycarbonyl)amino]heptyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 142-144 °C.

<u>Example 193:</u> (R,S)-*N*-benzyl-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Acetate. Melting point: 115-116 °C.

<u>Example 194:</u> 4-(2-{(1*S*)-1-[(*tert*-butoxycarbonyl)amino]propyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 138-140 °C.

<u>Example 195:</u> (R,S)-*N*-benzyl-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-heptanamine

Free base. Melting point: 100-102 °C.

<u>Example 196:</u> (1*S*)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-propanamine

Hydrochloride. Melting point: > 250 °C.

<u>Example 197:</u> *tert*-butyl (1*S*)-1-(4,5-diphenyl-1*H*-imidazol-2-yl)propylcarbamate

Free base. Melting point: 136-138 °C.

<u>Example 198:</u> (1*S*)-*N*-benzyl-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-propanamine

Free base. Melting point: 220-222 °C.

<u>Example 199:</u> (1*S*)-1-(4,5-diphenyl-1*H*-imidazol-2-yl)-1-propanamine

Hydrochloride. Melting point: 224-226 °C.

<u>Example 200:</u> (R,S)-*N*-benzyl-1-[4-(4-methylphenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Hydrochloride. Melting point: 185-188 °C.

<u>Example 201:</u> (R,S)-*N*-benzyl-1-[4-(2-methoxyphenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Free base. Melting point: 155-157 °C.

<u>Example 202:</u> (R,S)-*N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-hexanamine

Free base. Melting point: 192-194 °C.

<u>Example 203:</u> 4-[2-(2-{[(neopentyloxy)carbonyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl

Free base. Melting point: 162-164 °C.

<u>Example 204:</u> (1*S*)-*N*-benzyl-1-(4,5-diphenyl-1*H*-imidazol-2-yl)-1-propanamine

Free base. Melting point: 182-184 °C.

<u>Example 205:</u> (R,S)-4-[2-(1-aminoheptyl)-1*H*-imidazol-4-yl]benzonitrile

Hydrochloride. Melting point: 218-220 °C.

<u>Example 206:</u> (R,S)-1-[4-(4-bromophenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Free base. Melting point: from 126 °C.

<u>Example 207:</u> *tert*-butyl (1*R*)-1-(4-phenyl-1*H*-imidazol-2-yl)butylcarbamate

Free base. Melting point: 156-158 °C.

<u>Example 208:</u> 4-(2-{(1*R*)-1-[(*tert*-butoxycarbonyl)amino]butyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 145.6 °C.

<u>Example 209:</u> (1*R*)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-butanamine

Hydrochloride. Melting point: 155.4 °C.

<u>Example 210:</u> (R,S)-4-[2-(1-aminoheptyl)-1*H*-imidazol-4-yl]-2,6-di(*tert*-butyl)-phenol

Hydrochloride. Melting point: 204-206 °C.

<u>Example 211:</u> (1*R*)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-butanamine

Hydrochloride. Melting point: 182-184 °C.

<u>Example 212:</u> (R,S)-*N*-benzyl-1-[4-(4-bromophenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Free base. Melting point: becomes pasty from 130 °C.

<u>Example 213:</u> (1*R*)-*N*-benzyl-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)-1-butanamine

Free base. Melting point: 78.6 °C.

<u>Example 214:</u> (1*R*)-*N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-butanamine

Free base. Melting point: 218-220 °C.

<u>Example 215:</u> (R,S)-*N*-(3-chlorobenzyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine

Free base. The melting point could not be measured (paste).

<u>Example 216:</u> (R,S)-*N*-benzyl-1-[4-(3-methoxyphenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Free base. Melting point: 141-142 °C.

<u>Example 217:</u> (R,S)-4-{2-[1-(benzylamino)heptyl]-1*H*-imidazol-4-yl}benzonitrile

Free base. Melting point: 188-189 °C.

<u>Example 218:</u> (R,S)-4-[2-(1-aminoheptyl)-1*H*-imidazol-4-yl]-*N*,*N*-diethylaniline

Hydrochloride. Melting point: 192 °C.

<u>Example 219:</u> (1*R*)-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine

Hydrochloride. Melting point: 178-181 °C.

<u>Example 220:</u> (R,S)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Hydrochloride. Melting point: 148-150 °C.

<u>Example 221:</u> (R,S)-1-[4-(2-chlorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Hydrochloride. Melting point: 138-140 °C.

Example 222: ***N*-[(1*S*)-1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)propyl]-1-butanamine**

Free base. The melting point could not be measured (paste).

Example 223: **(1*R*)-*N*-benzyl-1-(4-phenyl-1*H*-imidazol-2-yl)ethanamine**

Free base. The melting point could not be measured (paste).

Example 224: **(R,S)-*N*-[1-(4-phenyl-1*H*-imidazol-2-yl)heptyl]-*N*-propylamine**

Free base. Melting point: 94-98 °C.

Example 225: **(R,S)-*N*-benzyl-1-[4-(3-methoxyphenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Hydrochloride. Melting point: from 120 °C.

Example 226: **(R,S)-4-{2-[1-(benzylamino)heptyl]-1*H*-imidazol-4-yl}benzonitrile**

Hydrochloride. Melting point: from 185 °C.

Example 227: **(R,S)-*N*-(4-methoxybenzyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine**

Free base. Melting point: 126-128 °C.

Example 228: **(R,S)-*N*-benzyl-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Hydrochloride. Melting point: from 110 °C.

Example 229: **(R,S)-*N*-benzyl-1-[4-(2-chlorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine**

Hydrochloride. Melting point: from 90 °C.

Example 230: **(R,S)-*N*-benzyl-*N*-(1-{4-[4-(diethylamino)phenyl]-1*H*-imidazol-2-yl}heptyl)amine**

Hydrochloride. Melting point: 170 °C.

<u>Example 231:</u> (R,S)-1-[4-(3,4-dichlorophenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Hydrochloride. Melting point: 148-150 °C.

<u>Example 232:</u> *tert*-butyl (R,S)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-5-methylhexylcarbamate

Free base. Melting point: 134-136 °C.

<u>Example 233:</u> (R,S)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-5-methyl-1-hexanamine

Hydrochloride. Melting point: 200-202 °C.

<u>Example 234:</u> (R,S)-*N*-isobutyl-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine

Acetate. Melting point: 70-72 °C.

<u>Example 235:</u> (R,S)-*N*-benzyl-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-5-methyl-1-hexanamine

Free base. Melting point: 92-94 °C.

<u>Example 236:</u> (R,S)-*N*-benzyl-1-[4-(4-methoxyphenyl)-1*H*-imidazol-2-yl]-1-heptanamine

Free base. Oil.

<u>Example 237:</u> 4-[2-(2-{[(benzyloxy)carbonyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl

Free base. Melting point: 134-136 °C.

<u>Example 238:</u> 4-(2-{1-[(butoxycarbonyl)amino]-1-methylethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 170-172 °C.

<u>Example 239:</u> 4-(2-{2-[(isobutoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 134-135 °C.

<u>Example 240:</u> (R,S)-*N*-[1-(4-phenyl-1*H*-imidazol-2-yl)heptyl]cyclobutanamine

Free base. Melting point: 148-150 °C.

<u>Example 241:</u> 4-(2-{(1*S*)-1-[(butoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 118-122 °C.

<u>Example 242:</u> 4-(2-{(1*R*)-1-[(butoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 114-116 °C.

<u>Example 243:</u> *N*-[(*S*)-cyclohexyl(4-phenyl-1*H*-imidazol-2-yl)methyl]-cyclohexanamine

Free base. Melting point: 240-242 °C.

<u>Example 244:</u> 4-(2-{2-[(methoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 177.2 °C.

<u>Example 245:</u> 4-(2-{2-[(propoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 141.2 °C.

<u>Example 246:</u> 4-(2-{2-[(ethoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl

Free base. Melting point: 132.5 °C.

<u>Example 247:</u> 4-[2-(1-{[(benzyloxy)carbonyl]amino}-1-methylethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl

Free base. Melting point: 148-152 °C.

<u>Example 248:</u> (R,S)-*N*-isopropyl-*N*-[1-(4-phenyl-1*H*-imidazol-2-yl)heptyl]amine

Free base. Melting point: 114-116 °C.

<u>Example 249:</u> ***N*-[2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethyl]-cyclohexanamine**

Free base. Melting point: 207-210 °C.

<u>Example 250:</u> **(R,S)-*N*-{1-[4-(3,4-dichlorophenyl)-1*H*-imidazol-2-yl]heptyl}-cyclohexanamine**

Hydrochloride. Melting point: 194 °C.

<u>Example 251:</u> **butyl 2-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethylcarbamate**

Free base. Melting point: 87 °C.

<u>Example 252:</u> **(R,S)-*N*-[1-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)heptyl]-cyclohexanamine**

Hydrochloride. Melting point: 168-170 °C.

<u>Example 253:</u> **(R,S)-2-(5-fluoro-1*H*-indol-3-yl)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethylamine**

Hydrochloride. Melting point: 220-222 °C.

<u>Example 254:</u> ***N*-{[4-(3-bromophenyl)-1*H*-imidazol-2-yl]methyl}cyclohexanamine**

Free base. Melting point: 202-204 °C.

<u>Example 255:</u> **hexyl 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 116.5-116.8 °C.

<u>Example 256:</u> **(R,S)-*N*-{2-(5-fluoro-1*H*-indol-3-yl)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethyl}cyclobutanamine**

Hydrochloride. Melting point: 180-190 °C.

<u>Example 257:</u> **(R,S)-*N*-{1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-4-methylpentyl}-cyclohexanamine**

Hydrochloride. Melting point: 230-232 °C.

<u>Example 258:</u> (*S*)-cyclohexyl[4-(3,4-difluorophenyl)-1*H*-imidazol-2-yl]-methanamine

Hydrochloride. Melting point: 222-223 °C.

<u>Example 259:</u> (*S*)-cyclohexyl[4-(3-fluoro-4-methoxyphenyl)-1*H*-imidazol-2-yl]-methanamine

Hydrochloride. Melting point: 225-227 °C.

<u>Example 260:</u> (R,S)-cyclopropyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-methanamine

Hydrochloride. Melting point: 230-232 °C.

<u>Example 261:</u> *N*-{(*S*)-cyclohexyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methyl}-2-propanamine

Free base. Melting point: 210-212 °C.

<u>Example 262:</u> *N*-{(*S*)-cyclohexyl[4-(3,4-difluorophenyl)-1*H*-imidazol-2-yl]methyl}cyclobutanamine

Free base. Melting point: 200-202 °C.

<u>Example 263:</u> (R,S) *N*-(cyclohexylmethyl)-1-(4-phenyl-1*H*-imidazol-2-yl)-1-heptanamine

Hydrochloride. Melting point: 142-144 °C.

<u>Example 264:</u> *N*-{(*S*)-cyclohexyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methyl}cyclohexanamine

Hydrochloride. Melting point: > 250 °C.

<u>Example 265:</u> (*S*)-cyclohexyl-*N*-(cyclohexylmethyl)(4-phenyl-1*H*-imidazol-2-yl)methanamine

Hydrochloride. Melting point: 180-182 °C.

<u>Example 266:</u> (R,S)-*N*-{cyclopropyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methyl}cyclohexanamine

Hydrochloride. The melting point could not be measured (paste).

<u>Example 267:</u> (*S*)-cyclohexyl-*N*-(cyclopropylmethyl)(4-phenyl-1*H*-imidazol-2-yl)methanamine

Hydrochloride. Melting point: 151-152 °C.

<u>Example 268:</u> butyl 2-[4-(4-cyclohexylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 138.4 °C.

<u>Example 269:</u> 4-[2-(2-{[(cyclohexyloxy)carbonyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl

Free base. Melting point: 150 °C.

<u>Example 270:</u> *N*-((*S*)-cyclohexyl{4-[4-(trifluoromethoxy)phenyl]-1*H*-imidazol-2-yl}methyl)-cyclobutanamine

Free base. Melting point: 136-140 °C.

<u>Example 271:</u> 4-[2-(2-{[(cyclopentyloxy)carbonyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl

Free base. Melting point: 140.5 °C.

<u>Example 272:</u> (R,S)-*N*-{1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-5-methylhexyl}-cyclohexanamine

Hydrochloride. Melting point: 216.7 °C.

<u>Example 273:</u> (*S*)-cyclohexyl-*N*-(cyclopropylmethyl)[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-methanamine

Hydrochloride. Melting point: 221.4 °C.

<u>Example 274:</u> (R,S)-*N*-{cyclopentyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methyl}cyclobutanamine

Free base. Melting point: 146-148 °C.

<u>Example 275:</u> ***N*-{(*S*)-cyclohexyl[4-(4-cyclohexylphenyl)-1*H*-imidazol-2-yl]methyl}cyclobutanamine**

Hydrochloride. Melting point: 190-192 °C.

<u>Example 276:</u> ***N*-{(1*R*)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-2-methylpropyl}-cyclohexanamine**

Free base. Melting point: 224-226 °C.

<u>Example 277:</u> ***N*-((*S*)-cyclohexyl{4-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}methyl)cyclobutanamine**

Acetate. Melting point: from 130 °C.

<u>Example 278:</u> **butyl 2-[4-(2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-imidazol-2-yl]ethylcarbamate**

Free base. Gum.

<u>Example 279:</u> ***N*-{(*S*)-cyclohexyl[4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-2-yl]methyl}cyclohexanamine**

Hydrochloride. Melting point: 190-194 °C.

<u>Example 280:</u> **cyclohexylmethyl 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 132-134 °C.

<u>Example 281:</u> **4-bromo-4'-(2-{2-[(butoxycarbonyl)amino]ethyl}-1*H*-imidazol-4-yl)-1,1'-biphenyl**

Free base. Melting point: 166 °C.

<u>Example 282:</u> ***N*-((*S*)-cyclohexyl{4-methylthiophenyl]-1*H*-imidazol-2-yl}methyl)cyclohexanamine**

Free base. Melting point: 96-98 °C.

<u>Example 283:</u> ***N*-{(*S*)-cyclohexyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methyl}-cyclohexanamine**

Free base. Melting point: 260-262 °C.

<u>Example 284:</u> ***N*-[(*S*)-{4-[3,5-bis(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}(cyclohexyl)methyl]cyclohexanamine**

Free base. Melting point: 180-182 °C.

<u>Example 285:</u> **cyclobutylmethyl 2-(4-[1,1'-biphenyl]-4-yl-1*H*-imidazol-2-yl)ethylcarbamate**

Free base. Melting point: 144-145 °C.

<u>Example 286:</u> **cyclobutylmethyl 2-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethylcarbamate**

Free base. Melting point: 149-150 °C.

<u>Example 287:</u> ***N*-{(*S*)-cyclohexyl[4-(3,4-difluorophenyl)-1*H*-imidazol-2-yl]methyl}cyclohexanamine**

Free base. Melting point: 182.3 °C.

<u>Example 288:</u> **4-[2-(2-{[(2-methoxyethoxy)carbonyl]amino}ethyl)-1*H*-imidazol-4-yl]-1,1'-biphenyl**

Free base. Melting point: 123.3 °C.

<u>Example 289:</u> **(*S*)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-1-cyclohexyl-*N*-(cyclohexylmethyl)methanamine**

Free base. Melting point: 134.3 °C.

<u>Example 290:</u> **4-(2-{(*S*)-cyclohexyl[(cyclohexylmethyl)amino]methyl}-1*H*-imidazol-4-yl)-*N*,*N*-diethylaniline**

Hydrochloride. Melting point: 204-206 °C.

<u>Example 291:</u> 2,6-di*tert*-butyl-4-(2-{(*S*)-cyclohexyl[(cyclohexylmethyl)amino]-methyl}-1*H*-imidazol-4-yl)phenol

Hydrochloride. Melting point: 254.6 °C.

<u>Example 292:</u> 4-{2-[(*S*)-cyclohexyl(cyclohexylamino)methyl]-1*H*-imidazol-4-yl}-*N*,*N*-diethylaniline

Hydrochloride. Melting point: 204-210 °C.

<u>Example 293:</u> (*S*)-1-cyclohexyl-*N*-(cyclohexylmethyl)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methanamine

Free base. Melting point: 184.8 °C.

<u>Example 294:</u> butyl 2-[4-(4-*tert*-butylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 106-108 °C.

<u>Example 295:</u> (*S*)-1-cyclohexyl-*N*-(cyclohexylmethyl)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methanamine

Hydrochloride. Melting point: 190-192 °C.

<u>Example 296:</u> *N*-((*S*)-cyclohexyl{4-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}methyl)cyclohexanamine

Hydrochloride. Melting point: 214.1 °C.

<u>Example 297:</u> *N*-[(*S*)-[4-(3-bromophenyl)-1*H*-imidazol-2-yl](cyclohexyl)methyl]-cyclohexanamine

Hydrochloride. Melting point: 230.4 °C.

<u>Example 298:</u> *N*-((*S*)-cyclohexyl{4-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}methyl)cyclohexanamine

Free base.

<u>Example 299:</u> butyl 2-[4-(4-bromophenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 99-100 °C.

Example 300: **butyl 2-{4-[4-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}ethylcarbamate**

Free base. Melting point: 104-105 °C.

Example 301: ***N*-{(*S*)-cyclohexyl[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methyl}cycloheptanamine**

Free base. Melting point: 140-142 °C.

Example 302: **cyclohexylmethyl 2-[4-(4-*tert*-butylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate**

Free base. Melting point: 104-106 °C.

Example 303: **cyclohexylmethyl 2-[4-(4'-bromo-1.1'-biphenyl-4-yl)-1*H*-imidazol-2-yl]ethylcarbamate**

Free base. Melting point: 130-132 °C.

Example 304: ***N*-((*S*)-cyclohexyl{4-[3-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}methyl)cyclohexanamine**

Free base. Melting point: 186-188 °C.

Example 305: **(*S*)-1-cyclohexyl-*N*-(cyclohexylmethyl)-1-{4-[3-(trifluoromethyl)-phenyl]-1*H*-imidazol-2-yl}methanamine**

Free base. Melting point: 143.9 °C.

Example 306: **(*S*)-1-[4-(3-bromophenyl)-1*H*-imidazol-2-yl]-1-cyclohexyl-*N*-(cyclohexylmethyl)methanamine**

Hydrochloride. Melting point: 206.3 °C.

Example 307: **(*S*)-1-cyclohexyl-*N*-(cyclohexylmethyl)-1-{4-[3-(trifluoromethyl)-phenyl]-1*H*-imidazol-2-yl}methanamine**

Hydrochloride. Melting point: 198-200 °C.

<u>Example 308:</u> (1*R*)-2-cyclohexyl-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethanamine

Hydrochloride. Melting point: 148-149 °C.

<u>Example 309:</u> *N*-{(1*R*)-2-cyclohexyl-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethyl}cyclohexanamine

Free base. Melting point: 217-218 °C.

<u>Example 310:</u> 4-{2-[(*S*)-amino(cyclohexyl)methyl]-1*H*-imidazol-4-yl}-*N*,*N*-diethylaniline

Hydrochloride. Melting point: 216-217 °C.

<u>Example 311:</u> (*S*)-1-cyclohexyl-1-[4-(3-fluorophenyl)-1*H*-imidazol-2-yl]methanamine

Hydrochloride. Melting point: 238-241 °C.

<u>Example 312:</u> (*S*)-1-cyclohexyl-*N*-(cyclohexylmethyl)-1-[4-(3-fluorophenyl)-1*H*-imidazol-2-yl]methanamine

Hydrochloride. Melting point: 180-186 °C.

<u>Example 313:</u> butyl 2-[4-(4-pyrrolidin-1-ylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 125 °C.

<u>Example 314:</u> *N*-{(*S*)-cyclohexyl[4-(3-fluorophenyl)-1*H*-imidazol-2-yl]methyl}cyclohexanamine

Hydrochloride. Melting point: 213.9 °C.

<u>Example 315:</u> *N*-{(1*R*)-2-cyclohexyl-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]ethyl}cyclohexanamine

Hydrochloride. Melting point: decomposes from 250 °C.

Example 316: **4-{2-[(*S*)-amino(cyclohexyl)methyl]-1*H*-imidazol-4-yl}-2,6-di*tert*-butylphenol**

Hydrochloride. Melting point: 222-228 °C.

Example 317: **butyl 2-[4-(4-pyrrolidin-1-ylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate**

Hydrochloride. Melting point: 165-166 °C.

Example 318: **(*R*)-1-cyclohexyl-*N*-(cyclohexylmethyl)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]methanamine**

Hydrochloride. Melting point: 188.2 °C.

Example 319: **2,6-di*tert*-butyl-4-[4-(hydroxymethyl)-1,3-thiazol-2-yl]phenol**

The compound of Example 319 can be obtained according to a protocol analogous to that described for the compound of Example 38, Stage E of PCT Patent Application WO 99/09829, except that ethyl bromopyruvate replaces the 3-chloroacetoacetate in Stage 38.C and that disobutylaluminium hydride replaces the lithium aluminium hydride in Stage 38.E.
Alternatively, this compound can also be obtained according to the procedure described in *J. Med. Chem.* (1996), **39**, 237-245. White solid. Melting point: 123-124 °C.

Example 320: ***meta*-[4-(2,3-dihydro-1H-indol-6-yl)-1,3-thiazol-2-yl]-N-methylmethanamine hydrochloride**

320.1) *Mixture of meta-2-chloro-1-[1-(chloroacetyl)-2,3-dihydro-1H-indol-6-yl]ethanone and para-2-chloro-1-[1-(chloroacetyl)-2,3-dihydro-1H-indol-6-yl]ethanone*

1-(chloroacetyl)-2,3-dihydro-1*H*-indole (3.9 g; 20 mmol) is dissolved in carbon disulphide (40 ml). $AlCl_3$ (6.15 g; 46 mmol) is added slowly then chloroacetyl chloride (1.835 ml; 22 mmol) is added dropwise to the mixture which is then heated under reflux for 18 hours. After the reaction medium is cooled down, the CS_2 is decanted and ice-cooled water containing concentrated HCl is added. After extraction with dichloromethane, the organic phase is separated and dried over magnesium sulphate before being filtered and concentrated under vacuum. The expected product (a 50/50

mixture of the meta and para isomers) is obtained by purification by crystallization from glacial acetic acid. White-coloured solid (1.6 g; yield of 30%).
MH+ = 271.

320.2) *meta-2-chloro-1-(2,3-dihydro-1H-indol-6-yl)ethanone hydrochloride*

Intermediate 320.1 (mixture of isomers; 1.6 g; 6.0 mmol) is dissolved hot in a mixture of acetic acid (10 ml) and 20% HCl (2 ml). The reaction medium is heated under reflux for 24 hours. After evaporation then purification by crystallization of the hydrochloride from glacial acetic acid in order to separate the mixture of isomers, the meta isomer crystallizes in the form of a brown solid (the para isomer remains in the mother liquors) with a yield of 47%. Melting point: decomposition from 158 °C.
MH+ = 196.
The meta structure of the compound was established by NMR/NOESY.

320.3) *meta-[4-(2,3-dihydro-1H-indol-6-yl)-1,3-thiazol-2-yl]-N-methylmethanamine hydrochloride*

The experimental protocol used is identical to that described for compound 30.2 of Example 30, intermediate 320.2 being used as the starting product instead of intermediate 30.1, tetrahydrofuran replacing the toluene in the presence of one equivalent of triethylamine in order to release the base of the salt. A brown-coloured solid is obtained with a yield of 9%. Melting point: decomposition from 235 °C.
MH+ = 246.

<u>Example 321:</u> 2,5,7,8-tetramethyl-2-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}-6-chromanol hydrochloride

321.1) *6-hydroxy-N-methoxy-N,2,5,7,8-pentamethyl-2-chromanecarboxamide*

2.2 g (22.0 mmol) of O,N-dimethylhydroxylamine hydrochloride, triethylamine (6.2 ml), 3.0 g (22.0 mmol) of hydroxybenzotriazole and 4.2 g (22.0 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride are added successively to a solution of 5.0 g (20.0 mmol) of (R,S) 6-hydroxy-2.5,7,8-tetramethyl-2-chromanecarboxylic acid (Trolox®) in 175 ml of DMF. After the reaction mixture is stirred overnight at 25 °C, the mixture is diluted with ice-cooled water and stirring is maintained for 30 more minutes. The product is extracted using 3 times 100 ml of ethyl acetate. The organic solution is washed successively with a 10% aqueous solution of sodium bicarbonate, with water, with a 10% aqueous solution of citric acid and finally with a saturated solution of sodium chloride. The organic phase is then dried over

magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from ether in order to produce a white-coloured solid with a yield of 63%. Melting point: 139-140 °C.
MH+ = 294.

321.2) *1-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromen-2-yl)ethanone*

A solution of methyllithium (1.6 M; 31.25 ml; 50.0 mmol) is added dropwise at a temperature of -30 °C to a solution of 2.93 g (10.0 mmol) of intermediate 321.1 in 100 ml of THF and the mixture is left under stirring for 1 hour at -10 °C. The reaction medium is hydrolyzed with NH_4Cl in a saturated aqueous solution. The product is extracted using 3 times 150 ml of ethyl acetate. The organic phase is finally washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from diisopropyl ether in order to produce a white solid with a yield of 80.7%. Melting point: 97-98 °C.
MH+ = 248.

321.3) *2-bromo-1-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-chromen-2-yl)ethanone*

Intermediate 321.2 (0.777 g; 3.13 mmol) is dissolved in ethanol (25 ml) under a stream of argon. The solution is cooled down to 0 °C and bromine (0.18 ml; 4.20 mmol) is added in one go (see *J. Am. Chem. Soc.* (1999), **121**, 24), then the mixture is stirred for 30 minutes allowing the temperature to rise to ambient temperature. The excess bromine is eliminated by bubbling through argon then the mixture is left under stirring for 2.5 hours. The ethanol is evaporated off and the product obtained is purified by crystallization from toluene. After filtering and washing with isopentane, a brown solid is obtained with a yield of 36%. Melting point: decomposition from 125 °C.
MH+ = 326.

321.4) *2,5,7,8-tetramethyl-2-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}-6-chromanol hydrochloride*

The experimental protocol used is analogous to that described for compound 30.2 of Example 30, intermediate 321.3 being used as the starting product instead of intermediate 30.1, and benzene replacing the toluene as solvent. The product obtained is purified by crystallization from a minimum amount of dichloromethane in order to produce a white solid with a yield of 48%. Melting point: 153-155 °C.

<u>Example 322:</u> *N*-{[4-(9*H*-carbazol-2-yl)-1,3-thiazol-2-yl]methyl}-*N*-methylamine hydrochloride

322.1) *9-acetyl-9H-carbazole*

This compound is obtained according to *Tetrahedron* (1980), **36**, 3017-3019. The carbazole (10 g; 60 mmol) is suspended in 150 ml of acetic anhydride. 70% perchloric acid (0.5 ml) is added. After stirring for 30 minutes at ambient temperature, the mixture is poured into ice and the precipitate formed is filtered. After drying under vacuum, redissolving in dichloromethane and treatment with bone charcoal, the suspension is filtered on celite, the solvents are evaporated off and the product recrystallized from heptane. 12 g of brown crystals (yield of 90%) is obtained in this way. Melting point: 70-71 °C (literature: 72-74 °C).

322.2) *1-(9-acetyl-9H-carbazol-2-yl)-2-chloroethanone*

This compound is obtained according to a protocol analogous to that of Stage 320.1 of Example 320, using 5 g (24 mmol) of intermediate 322.1. 5.4 g of the expected compound is obtained (yield of 79%). White solid. Melting point: 175-176 °C.

322.3) *1-(9H-carbazol-2-yl)-2-chloroethanone*

Intermediate 322.2 (2.85 g;1 mmol) is suspended in a mixture of acetic acid (50 ml) and concentrated HCl (5 ml). The reaction medium is heated under reflux for 2 hours before being left to return to ambient temperature. The new precipitate formed is filtered. After drying under vacuum, 1.9 g of a greenish solid is obtained (yield of 78%). Melting point: 203-204 °C.

322.4) *N-{[4-(9H-carbazol-2-yl)-1,3-thiazol-2-yl]methyl}-N-methylamine hydrochloride*

This compound is obtained according to a protocol analogous to that of Stage 30.2 from 487 mg (2 mmol) of intermediate 322.3 and 408 mg (2 mmol) of *tert*-butyl 2-amino-2-thioxoethyl(methyl)carbamate. 300 mg of the expected product is obtained (yield of 43%). White solid. Melting point: > 250 °C.

Example 323: 3,5-ditert-butyl-4'-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}-1,1'-biphenyl-4-ol hydrochloride

323.1) *3',5'-ditert-butyl-4'-hydroxy-1,1'-biphenyl-4-carboxylic acid*

5.0 g (1.41 mmol) of ethyl 3',5'-ditert-butyl-4'-hydroxy-1,1'-biphenyl-4-carboxylate (*Chem. Lett.* (1998), **9**, 931-932) is dissolved in ethanol (25 ml). The solution is cooled down to 0 °C then a 1*N* solution of soda is added dropwise. After stirring overnight at ambient temperature, the reaction medium is heated under reflux in order to complete the reaction. After evaporation of the solvents and dilution of the residue with water, the mixture obtained is acidified with a 1*N* solution of HCl and extraction is carried out with dichloromethane. The organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from diisopropyl ether in order to produce a yellow-white solid with a yield of 47%. Melting point: >240 °C.

323.2) *3',5'-ditert-butyl-4'-hydroxy-N-methoxy-N-methyl-1,1'-biphenyl-4-carboxamide*

The experimental protocol used is identical to that described for intermediate 321.1, with acid 323.1 replacing the Trolox® as starting product. A yellowish solid is obtained with a yield of 93%. Melting point: 175.6-177 °C.

323.3) *1-(3',5'-ditert-butyl-4'-hydroxy-1,1'-biphenyl-4-yl)ethanone*

The experimental protocol used is identical to that described for intermediate 321.2, intermediate 323.2 replacing intermediate 321.1. A white solid is obtained with a yield of 74%. Melting point: 144-144.7 °C.

323.4) *2-bromo-1-(3',5'-ditert-butyl-4'-hydroxy-1,1'-biphenyl-4-yl)ethanone*

The experimental protocol used is identical to that described for intermediate 321.3, intermediate 323.3 replacing intermediate 321.2. A yellow-orange oil is obtained which is sufficiently pure to be used in the following stage (yield of 100%).

323.5) *tert-butyl [4-(3',5'-ditert-butyl-4'-hydroxy-1,1'-biphenyl-4-yl)-1,3-thiazol-2-yl]methyl(methyl)carbamate*

This compound is prepared according to the experimental protocol described in Example 1, Stage 1.3, using intermediate 323.4 instead of bromo-1-(3,5-ditert-butyl-

4-hydroxyphenyl)ethanone. The expected compound is obtained in the form of a colourless oil with a yield of 46%.
MH+ = 509.43.

323.6) *3,5-ditert-butyl-4'-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}-1,1'-biphenyl-4-ol hydrochloride*

0.230 g (0.452 mmol) of intermediate 323.5 is dissolved in ethyl acetate (20 ml). HCl gas is bubbled through the solution previously obtained cooled down to 0 °C. The stirred mixture is then allowed to return to ambient temperature. The solid formed is filtered and washed with ethyl acetate then with ether before being dried under vacuum. A white solid is obtained with a yield of 85%. Melting point: 220-221 °C.

The compounds of Examples 324 to 330 are obtained according to procedures analogous to those described for Examples 31 to 46 or above in the part entitled "Preparation of compounds of general formula (I)".

<u>Example 324:</u> (1R)-1-[4-(4-fluorophenyl)-1H-imidazol-2-yl]-2-phenylethanamine

Hydrochloride. Melting point: 173-180 °C.

<u>Example 325:</u> cyclohexylmethyl 2-{4-[4-(diethylamino)phenyl]-1H-imidazol-2-yl}ethylcarbamate

Hydrochloride. Melting point: decomposes from 168 °C.

<u>Example 326:</u> cyclohexylmethyl 2-[4-(4-pyrrolidin-1-ylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 128.5 °C.

<u>Example 327:</u> *N*-{(1*R*)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-2-phenylethyl}cyclohexanamine

Hydrochloride. Melting point: 210-213 °C.

<u>Example 328:</u> (1*R*)-*N*-(cyclohexylmethyl)-1-[4-(4-fluorophenyl)-1*H*-imidazol-2-yl]-2-phenylethanamine

Hydrochloride. Melting point: from 140 °C.

Example 329: cyclohexylmethyl 2-[4-(3,5-di*tert*-butyl-4-hydroxyphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Hydrochloride. Melting point: 111.5 °C.

Example 330: butyl 2-[4-(3,5-di*tert*-butyl-4-hydroxyphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 180.9 °C.

Example 331: 2,6-dimethoxy-4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride

331.1) *4-acetyl-2,6-dimethoxyphenyl acetate*

3.0 g (15.3 mmol) of 3,5-dimethoxy-4-hydroxyacetophenone is dissolved in dichloromethane (30 ml) and 2.53 g (18.3 mmol) of K_2CO_3 is added. Triethylamine (2.6 ml) is then added dropwise. The reaction medium is cooled down to 0 °C and acetyl chloride (1.31 ml; 18.3 mmol) is added. The mixture is stirred for 24 hours at ambient temperature then poured into ice-cooled water. After extraction with dichloromethane, the organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from ether in order to produce a white solid with a yield of 99%. Melting point: 145 °C.

331.2) *4-(bromoacetyl)-2,6-dimethoxyphenyl acetate*

Intermediate 331.1 (0.850 g; 3.57 mmol) is solubilized in ethyl acetate then 1.35 g (6.07 mmol) of previously dried $CuBr_2$ is added. The mixture is heated under reflux for 2.5 hours before being left to return to ambient temperature. Ground charcoal is added and the mixture is stirred for 10 minutes. After filtering and evaporating to dryness, the solid obtained is taken up in diisopropyl ether. After filtering, a grey solid is obtained with a yield of 75%. Melting point: 124.2-126.3 °C.

331.3) *4-(2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-1,3-thiazol-4-yl)-2,6-dimethoxyphenyl acetate*

Intermediate 331.3 is prepared according to an experimental protocol described in Example 1, Stage 1.3, using intermediate 331.2 instead of bromo-1-(3,5-ditert-butyl-4-hydroxyphenyl)ethanone. The expected compound is obtained in the form of a white solid with a yield of 55%. Melting point: 135.2-137.4 °C.

331.4) *tert-butyl [4-(4-hydroxy-3,5-dimethoxyphenyl)-1,3-thiazol-2-yl]methyl(methyl)carbamate*

0.530 g (1.25 mmol) of intermediate 331.3 is dissolved in methanol (20 ml). The solution is cooled down using an ice bath then a 1*N* solution of NaOH is added dropwise. The mixture is left to return to ambient temperature under stirring. After evaporation to dryness and dilution of the residue with water, the solution is neutralised using citric acid followed by extraction with dichloromethane. The organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product is obtained in the form of a yellow oil with a yield of 96%.
MH+ = 381.20.

331.5) *2,6-dimethoxy-4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride*

The experimental protocol used is identical to that described for intermediate 323.6, intermediate 331.4 replacing intermediate 323.5. A light beige solid is obtained with a yield of 97%. Melting point: 229.8-232.0 °C.

<u>Example 332:</u> **2,6-diisopropyl-4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride**

332.1) *2,6-diisopropylphenyl acetate*

3.45 g (16.4 mmol) of trifluoroacetic anhydride is added to 0.83 ml (14.6 mmol) of acetic acid at 0 °C while leaving the mixture to return to ambient temperature over 2 hours. The mixture is then cooled down to 0 °C and 1.95g (11.0 mmol) of 2,6-diisopropylphenol is added dropwise. The reaction medium is maintained under stirring for 12 hours before being poured into ice-cooled water. After extraction with dichloromethane, the organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. A colourless oil is obtained with a yield of 86%. This product is sufficiently pure to be used directly in the following stage.

332.2) *1-(4-hydroxy-3,5-diisopropylphenyl)ethanone acetate*

1.94 g (14.53 mmol) of $AlCl_3$ is dissolved in nitrobenzene (5 ml). At the same time, 2.0 g (9.08 mmol) of intermediate 332.1 is dissolved in nitrobenzene (1 ml). The solution of intermediate 332.1 is added dropwise to the solution of $AlCl_3$ at ambient

temperature. The mixture is taken to 50 °C for 48 hours before being left to return to ambient temperature. The reaction medium is then poured into ice-cooled water. A 1*N* solution of HCl (5 ml) and then a concentrated solution of HCl (2 ml) are added. The mixture is stirred at ambient temperature followed by extraction with dichloromethane. The organic phase is washed with sodium chloride in a saturated aqueous solution before being dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 13% of ethyl acetate in heptane). After evaporation, the pure fractions produce a grey-white solid with a yield of 25%. Melting point: 88-93 °C.

332.3) *4-acetyl-2,6-diisopropylphenyl acetate*

The experimental protocol used is identical to that described for intermediate 331.1, intermediate 332.2 replacing the 3,5-dimethoxy-4-hydroxyacetophenone. A sand-coloured solid is obtained with a yield of 95%. Melting point: 102-103 °C.

332.4) *4-(bromoacetyl)-2,6-diisopropylphenyl acetate*

The experimental protocol used is identical to that described for intermediate 331.2, intermediate 332.3 replacing intermediate 331.1. A yellow oil is obtained which crystallizes slowly with a yield of 88%. This product is sufficiently pure to be used directly in the following stage.

332.5) *4-(2-{[(tert-butoxycarbonyl)(methyl)amino]methyl}-1,3-thiazol-4-yl)-2,6-diisopropylphenyl acetate*

Intermediate 332.5 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using intermediate 332.4 instead of the bromo-1-(3,5-ditert-butyl-4-hydroxyphenyl)ethanone. The expected compound is obtained in the form of a pale yellow solid with a yield of 76%.
MH+ = 447.20.

332.6) *tert-butyl [4-(4-hydroxy-3,5-diisopropylphenyl)-1,3-thiazol-2-yl]methyl(methyl)carbamate acetate*

The experimental protocol used is identical to that described for intermediate 331.4, intermediate 332.5 replacing intermediate 331.3. An ochre oil is obtained with a yield of 91%. This product is sufficiently pure to be used directly in the following stage.
MH+ = 405.20.

332.7) *2,6-diisopropyl-4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride*

The experimental protocol used is identical to that described for intermediate 323.6, intermediate 332.6 replacing intermediate 323.5. A beige-pink solid is obtained with a yield of 69%. Melting point: loses its colour at 162 °C and melts at 173-177 °C.

<u>Example 333:</u> 4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride

333.1) *2-bromo-1-(4-hydroxyphenyl)ethanone*

The experimental protocol used is identical to that described for intermediate 331.2, 4-hydroxy-acetophenone replacing intermediate 331.1. A brown-pink solid is obtained with a yield of 60%. Melting point: 118 °C.

333.2) *tert-butyl [4-(4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl(methyl)carbamate*

Intermediate 333.2 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using intermediate 333.1 instead of the bromo-1-(3,5-di*tert*-butyl-4-hydroxyphenyl)ethanone and toluene replacing the benzene. The expected compound is obtained in the form of a clear-yellow oil which very slowly crystallizes cold with a yield of 35%.
MH+ = 321.30.

333.3) *4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride*

The experimental protocol used is identical to that described for intermediate 323.6, intermediate 333.2 replacing intermediate 323.5. A pale yellow solid is obtained with a yield of 100%. Melting point: 258-260 °C.

<u>Example 334:</u> 2,6-ditert-butyl-4-[2-(hydroxymethyl)-1,3-thiazol-4-yl]phenol

[*this is intermediate 6.d$_1$) of Patent Application EP 432 740*]

334.1) *[4-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl pivalate*

Intermediate 334.1 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using 2-(*tert*-butylcarbonyloxy)thioacetamide instead of the 2-{[(1,1-dimethylethoxy)carbonyl]methyl}amino-ethanethioamide and toluene replacing the benzene. The expected compound is obtained in the form of a white solid with a yield of 100%. Melting point: 114.6-116.0 °C.

334.2) *2,6-ditert-butyl-4-[2-(hydroxymethyl)-1,3-thiazol-4-yl]phenol*

The experimental protocol used is identical to that described for intermediate 331.4, intermediate 334.1 replacing intermediate 331.3. A white solid is obtained with a yield of 88%. Melting point: 126.4-127.4 °C.

<u>Example 335</u>: N-{[4-(4-anilinophenyl)-1,3-thiazol-2-yl]methyl}-N-methylamine hydrochloride

335.1) *1-(4-anilinophenyl)ethanone*

4-amino-acetophenone (4.87 g; 36.0 mmol) is dissolved in dimethylformamide (75 ml). 15 g (0.108 mol) of potassium carbonate (previously dried at 170 °C under an argon atmosphere), 7.236 g (36.0 mmol) of iodobenzene, 0.4 g of copper powder and a catalytic quantity of copper iodide are added. The reaction mixture is taken to reflux for 12 hours. After leaving the reaction medium to return to ambient temperature, the latter is filtered on celite and poured into ice-cooled water. After extraction with ethyl acetate, the organic phase is washed with water before being dried over magnesium sulphate, filtered and concentrated under vacuum. The product obtained is purified by crystallization from heptane in order to produce a yellow solid with a yield of 53.4%. Melting point: 105 °C.

335.2) *N-(4-acetylphenyl)-N-phenylacetamide*

The experimental protocol used is identical to that described for intermediate 322.1, with intermediate 335.1 replacing the 9-acetyl-9H-carbazole and the reaction medium being however heated for 15 minutes at 70 °C. After crystallization from heptane, a yellow solid is obtained with a yield of 54.2%. Melting point: 118-120 °C (value in the literature: 122-123 °C).

335.3) *N-[4-(bromoacetyl)phenyl]-N-phenylacetamide*

Intermediate 335.2 (0.633 g; 2.5 mmol) is dissolved in methanol (20 ml) and 1 g (2.0 mmol) of bromination resin PVPHP (*J. Macromol. Sci. Chem.* (1977), **A11**, (3), 507-514) is added. After stirring under an argon atmosphere for 4 hours, filtration is carried out and the resins are rinsed with methanol. After evaporation of the filtrate solvents and crystallization from methanol, a white solid is obtained with a yield of 59%. Melting point: 152-153 °C.

335.4) *tert-butyl (4-{4-[acetyl(phenyl)amino]phenyl}-1,3-thiazol-2-yl)methyl(methyl)carbamate*

Intermediate 335.4 is prepared according to a protocol identical to that described for Example 1, Stage 1.3, using intermediate 335.3 instead of the bromo-1-(3,5-ditert-butyl-4-hydroxyphenyl)ethanone and toluene replacing the benzene. The expected compound is obtained in the form of an oil with a yield of 73%.
MH+ = 438.30.

335.5) *N-(4-{2-[(methylamino)methyl]-1,3-thiazol-4-yl}phenyl)-N-phenylacetamide hydrochloride*

The experimental protocol used is identical to that described for intermediate 322.3, intermediate 335.4 replacing intermediate 322.2. A white-cream solid is obtained with a yield of 53%. Melting point: > 250 °C.

335.6) *N-{[4-(4-anilinophenyl)-1,3-thiazol-2-yl]methyl}-N-methylamine hydrochloride*

The experimental protocol used is identical to that described for intermediate 322.3, intermediate 335.5 replacing intermediate 322.2 and the reaction medium being heated under reflux for 12 hours instead of 2 hours. A grey solid is obtained with a yield of 68%. Melting point: > 250 °C.

<u>Example 336</u>: 2,6-ditert-butyl-4-{2-[(dimethylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride

336.1) *4-[2-(bromomethyl)-1,3-thiazol-4-yl]-2,6-ditert-butylphenol*

1.5 g (4.70 mmol) of intermediate 334.2, (2,6-ditert-butyl-4-[2-(hydroxymethyl)-1,3-thiazol-4-yl]phenol is dissolved in dichloromethane (30 ml). After adding CBr_4 (2.02 g; 6.10 mmol), the reaction medium is cooled down to 0 °C. PPh_3 (1.48 g; 5.63 mmol) is added by fractions then the mixture is left to return to ambient temperature. The reaction medium is then poured into ice-cooled water before being extracted with dichloromethane. The organic phase is washed with salt water before being dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 30% of ethyl acetate in heptane), in order to produce a brown oil with a yield of 92%. This product is sufficiently pure to be used directly in the following stage.
MH+ = 382.20.

336.2) *2,6-ditert-butyl-4-{2-[(dimethylamino)methyl]-1,3-thiazol-4-yl}phenol hydrochloride*

0.8 ml (1.57 mmol) of dimethylamine and 0.4 ml (2.62 mmol) of triethylamine are dissolved in dimethylformamide (15 ml). 0.400 g (1.05 mmol) of intermediate 336.1 dissolved in dimethylformamide (5 ml) is added then the mixture is stirred at ambient temperature for 18 hours. The reaction medium is then poured into ice-cooled water followed by extraction with ethyl acetate. The organic phase is washed with salt water before being dried over magnesium sulphate, filtered and concentrated under vacuum. The expected product is obtained after chromatography on a silica column (eluent: 50% of ethyl acetate in heptane), in order to produce an orange oil with a yield of 92%. The hydrochloride is then obtained by solubilizing the base in ether and adding 1.2 ml of a 1*N* solution of HCl in ether. After filtering and washing of the solid formed with ether then with isopentane, a beige-pink solid is obtained with a yield of 15.2%. Melting point: 166.8-169.0 °C.

The compounds of Examples 337 to 345 are obtained according to procedures analogous to those described for Examples 31 to 46 or above in the part entitled "Preparation of compounds of general formula (I)".

Example 337: cyclobutylmethyl 2-[4-(4'-bromo-1,1'-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate

Hydrochloride. Melting point: 214-215 °C.

Example 338: isobutyl 2-[4-(4'-bromo-1,1'-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 158.7 °C.

Example 339: isobutyl 2-[4-(4-*tert*-butylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 110.6 °C.

Example 340: cyclobutylmethyl 2-[4-(4-*tert*-butylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 103 °C.

Example 341: cyclohexyl 2-[4-(4'-bromo-1.1'-biphenyl-4-yl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 180 °C.

Example 342: cyclohexyl 2-[4-(4-*tert*-butylphenyl)-1*H*-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 127-130 °C.

Example 343: 3-[4-(4-fluorophenyl)-1H-imidazol-2-yl]propan-1-amine

Hydrochloride. Melting point: 245-246 °C.

Example 344: 4,4,4-trifluorobutyl 2-[4-(4'-bromo-1,1'-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 176.5 °C.

Example 345: 4,4,4-trifluorobutyl 2-[4-(1,1'-biphenyl-4-yl)-1H-imidazol-2-yl]ethylcarbamate

Free base. Melting point: 157.3 °C.

Example 346: 2,6-ditert-butyl-4-{4-[(methylamino)methyl]-1,3-thiazol-2-yl}phenol hydrochloride

346.1) *4-[4-(bromomethyl)-1,3-thiazol-2-yl]-2,6-ditert-butylphenol*

The experimental protocol used is identical to that described for intermediate 336.1, the compound of Example 319 replacing intermediate 334.2, 1,2-dichloroethane replacing the dimethylformamide and the reaction medium being heated under reflux for 12 hours. A reddish oil is obtained with a yield of 77%. This product is used as it is directly in the following stage.

346.2) *2,6-ditert-butyl-4-{4-[(methylamino)methyl]-1,3-thiazol-2-yl}phenol*

The experimental protocol used is identical to that described for intermediate 336.2, intermediate 346.1 replacing intermediate 336.1, a 2*N* solution of methylamine in tetrahydrofuran replacing the dimethylamine and acetonitrile replacing the dimethylformamide. The hydrochloride is obtained by solubilizing the base in ether and adding a 1*N* solution of HCl in ether. The solid formed is filtered and purified by

recrystallization from acetone in order to produce a white solid with a yield of 18%. Melting point: 184.0-185.0 °C.

<u>Example 347:</u> 2,6-ditert-butyl-4-[2-(piperidin-1-ylmethyl)-1,3-thiazol-4-yl]phenol hydrochloride

The experimental protocol used is identical to that described for intermediate 336.2, piperidine replacing the dimethylamine. A white solid is obtained with a yield of 56%. Melting point: > 195 °C.

<u>Example 348:</u> 2,6-ditert-butyl-4-{2-[(4-methylpiperazin-1-yl)methyl]-1,3-thiazol-4-yl}phenol hydrochloride

The experimental protocol used is identical to that described for intermediate 336.2, N-methylpiperazine replacing the dimethylamine. A light brown solid is obtained with a yield of 62%. Melting point: 234.6-235.2 °C.

<u>Example 349:</u> 2,6-ditert-butyl-4-[2-(piperazin-1-ylmethyl)-1,3-thiazol-4-yl]phenol hydrochloride

349.1) *tert-butyl 4-{[4-(3,5-ditert-butyl-4-hydroxyphenyl)-1,3-thiazol-2-yl]methyl}piperazine-1-carboxylate*

The experimental protocol used is identical to that described for intermediate 336.2, N-Boc-piperazine replacing the dimethylamine. A pale orange solid is obtained with a yield of 64%. Melting point: 108-109 °C.

349.2) *2,6-ditert-butyl-4-[2-(piperazin-1-ylmethyl)-1,3-thiazol-4-yl]phenol hydrochloride*

The experimental protocol used is identical to that described for intermediate 323.6, intermediate 349.1 replacing intermediate 323.5. A white solid is obtained with a yield of 86%. Melting point: 255.4-257.7 °C.

Pharmacological study of the products of the invention

Study of the effects on the bond of a specific ligand of MAO-B, [^{3}H]Ro 19-6327

The inhibitory activity of the products of the invention is determined by measurement of their effects on the bond of a specific ligand of MAO-B, [^{3}H]Ro 19-6327.

a) *Mitochondrial preparation of the cortex of rats*

The mitochondrial preparation of the cortex of rats is carried out according to the method described in Cesura A M, Galva M D, Imhof R and Da Prada M, *J. Neurochem.* **48** (1987), 170-176. The rats are decapitated and their cortex is removed, homogenized in 9 volumes of a 0.32 M sucrose buffer, buffered to pH 7.4 with 5 mM of HEPES, then centrifuged at 800 g for 20 minutes. The supernatants are recovered and the pellets are washed twice with the 0.32 M sucrose buffer as previously. The collected supernatants are centrifuged at 10000g for 20 minutes. The pellets obtained are suspended in a Tris buffer (50 mM Tris, 130 mM NaCl, 5 mM KCl, 0.5 mM EGTA, 1 mM $MgCl_2$, pH 7.4) and centrifuged at 10000g for 20 minutes. This stage is repeated twice, and the final pellet, corresponding to the mitochondrial fraction, is stored at –80 °C in the Tris buffer. The proteinic content of the preparation is determined by the Lowry method.

b) *Bond of [^{3}H]Ro 19-6327*

100 µl of the mitochondrial preparation (2 mg protein/ml) are incubated for 1 hour at 37 °C in an Eppendorf tube, in the presence of 100 µl of [^{3}H] Ro 19-6327 (33 nM, final concentration) and 100 µl of Tris buffer containing or not containing the inhibitors. The reaction is stopped by the addition of 1 ml of unlabelled Tris buffer into each tube, then the samples are centrifuged for 2 minutes at 12000 g. The supernatants are removed by suction and the pellets washed with 1 ml of Tris buffer. The pellets are then solubilized in 200 µl of sodium dodecyl sulphate (20% weight/volume) for 2 hours at 70 °C. The radioactivity is determined by counting the samples using liquid scintillation.

c) *Results*

The compounds of Examples 1, 3, 6, 22, 24, 26 to 29, 323 and 332 described above show an IC_{50} lower than 10 µM.

Study of the effects on lipidic peroxidation of the cerebral cortex of the rat

The inhibitory activity of the products of the invention is determined by measuring their effects on the degree of lipidic peroxidation, determined by the concentration of

malondialdehyde (MDA). The MDA produced by peroxidation of unsaturated fatty acids is a good indication of lipidic peroxidation (H Esterbauer and KH Cheeseman, *Meth. Enzymol.* (1990) **186**: 407-421). Male Sprague Dawley rats weighing 200 to 250 g (Charles River) were sacrificed by decapitation. The cerebral cortex is removed, then homogenized using a Thomas potter in a 20 mM Tris-HCl buffer, pH = 7.4. The homogenate is centrifuged twice at 50000 g for 10 minutes at 4°C. The pellet is stored at -80°C. On the day of the experiment, the pellet is resuspended at a concentration of 1 g/ 15 ml and centrifuged at 515 g for 10 minutes at 4° C. The supernatant is used immediately to determine the lipidic peroxidation. The homogenate of rat's cerebral cortex (500 μl) is incubated at 37°C for 15 minutes in the presence of the compounds to be tested or of the solvent (10 μl). The lipidic peroxidation reaction is initiated by adding 50 μl of $FeCl_2$ at 1 mM, EDTA at 1 mM and ascorbic acid at 4 mM. After incubation for 30 minutes at 37°C, the reaction is stopped by adding 50 μl of a solution of hydroxylated di-tert-butyl toluene (BHT, 0.2 %). The MDA is quantified using a colorimetric test, by reacting a chromogenic reagent (R), N-methyl-2-phenylindol (650 μl) with 200 μl of the homogenate for 1 hour at 45° C. The condensation of an MDA molecule with two molecules of reagent R produces a stable chromophore the maximum absorbence wavelength of which is equal to 586 nm. (Caldwell et al. *European J. Pharmacol.* (1995) **285**, 203-206). The compounds of Examples 1 to 3, 6 to 17, 20 to 30, 320, 321, 323, 331 and 332 described above show an IC_{50} lower than 10 μM.

<u>Bond test on the cerebral sodium channels of the cortex of the rat</u>

The test consists in measuring the interaction of the compounds vis-à-vis the bond of tritiated batrachotoxin on the voltage-dependent sodium channels according to the protocol described by Brown (*J. Neurosci.* (1986), **6**, 2064-2070).

Preparation of homogenates of cerebral cortices of the rat

The cerebral cortices of Sprague-Dawley rats weighing 230-250 g (Charles River, France) are removed, weighed and homogenized using a Potter homogenizer provided with a teflon piston (10 strokes) in 10 volumes of isolation buffer the composition of which is as follows (sucrose 0.32 M; K_2HPO_4 5 mM; pH 7.4). The homogenate is subjected to a first centrifugation at 1000 g for 10 minutes. The supernatant is removed and centrifuged at 20000 g for 15 minutes. The pellet is taken up in the isolation buffer and centrifuged at 20000 g for 15 minutes. The pellet obtained is resuspended in incubation buffer (HEPES 50 mM; KCl 5.4 mM; $MgSO_4$ 0.8 mM; glucose 5.5 mM; choline chloride 130 mM pH 7.4) then aliquoted and stored at –80 °C until the day of

assay. The final protein concentration is comprised between 4 and 8 mg/ml. The assay of proteins is carried out using a kit marketed by BioRad (France).

Measurement of the bond of tritiated batrachotoxin

The bond reaction is carried out by incubating for 1 hour 30 minutes at 25 °C 100 µl of homogenate of rat cortex containing 75 µg of proteins with 100 µl of [^{3}H] batrachotoxin-A 20-alpha benzoate (37.5 Ci/mmol, NEN) at 5 nM (final concentration), 200 µl of tetrodotoxin at 1 µM (final concentration) and scorpion venom at 40 µg/ml (final concentration) and 100 µl of incubation buffer alone or in the presence of the products to tested at different concentrations. The non-specific bond is determined in the presence of 300 µM of veratridine and the value of this non-specific bond is subtracted from all the other values. The samples are then filtered using a Brandel (Gaithersburg, Maryland, USA) using Unifilter GF/C plates pre-incubated with 0.1 % of polyethylene imine (20 µl/well) and rinsed twice with 2 ml of filtration buffer (HEPES 5 mM; $CaCl_2$ 1.8 mM; $MgSO_4$ 0.8 mM; choline chloride 130 mM; BSA 0.01 %; pH 7.4). After having added 20 µl of Microscint 0 ®, the radioactivity is counted using a liquid scintillation counter (Topcount, Packard). The measurement is carried out in duplicate. The results are expressed as a % of the specific bond of tritiated batrachotoxin relative to the control.

Results

The compounds of Examples 1, 6, 7, 11, 13, 15, 17, 20, 24, 31 to 38, 42, 43, 46 to 48, 53, 56, 57, 59 to 61, 64 to 80, 82 to 88, 92 to 95, 97, 105, 106, 108, 110, 113, 117, 118, 121 to 123, 125, 128, 130 to 139, 142 to 145, 149, 151, 152, 154, 162 to 166, 168 to 178, 181, 183 to 186, 188, 190 to 196, 198 to 206, 208 to 210, 212 to 218, 220 to 231, 233 to 250, 252 to 259, 261 to 281, 283 to 288, 293 to 313, 324 and 338 to 340 described above all show an IC_{50} lower than or equal to 1 µM. Moreover, the compounds of Examples 3, 9, 10, 26, 28 to 30 and 321 described above show an IC_{50} lower than or equal to 3.5 µM.